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SOME STUDIES OF THE FORMULATION AND EVALUATION OF TABLETS WITH SPECIAL REFERENCE TO DIRECT COMPRESSION SUGARS

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ABSTRACT

The potential of several new sugar matrices as direct compression vehicles has been investigated using a systematically organized series of tests. These matrices, produced by California and Hawaiian Sugar Company (C & H), were evaluated in a comparative manner with two commercially available products (DiPac and NuTab). In some cases, Emdex (another commercially available product) was also used. Moisture content, density, and flow properties were studied. Scanning electron micrographs were obtained to determine the morphology of the particles. Particles size spectra were generated for all the matrices. For some of the C & H Products (AI, B, and C), a computer-interfaced instrumented tablet press was used to generate compression profiles from which the compressibility of the materials was assessed.

The formulation efficiency of four C & H Products (AI, AII, B, and Brown), DiPac, and NuTab was determined by incorporating the matrices in several chewable formulations (ascorbic acid, multivitamin, dextromethorphan, antihistamine, antidiarrhea, and antacid) and one non-chewable formulation (pediatric strength aspirin). A computer-interfaced tablet press, from which compression peak heights were obtained, was used to prepare the ascorbic acid, multivitamin, and aspirin tablets. The results show that the C & H matrices, particularly Product B, have considerable potential as direct compression vehicles. It was also demonstrated that the utility of sugar matrices is not limited to the formulation of chewable tablets. Further, the results indicate that although matrices maybe chemically alike, differences in their physical properties may indeed produce substantial differences in their intrinsic properties and overall formulation behavior.

The effect of aging on in-vitro performance of the antacid tablets was evaluated. It was found that samples stored under relatively mild stress conditions ($30^{o}C$ with 80% relative humidity) for three months had reduced acid neutralization rates. It was also found that these storage conditions were sufficient to induce substantial aging in sugar coated and enteric coated tablets (chlorpromazine and aspirin respectively) over a four week period.

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PLAN OF THE THESIS

This manuscript is divided into seven sections, numbered in Roman numerals. The sections are: I. Introduction, II. Experimental, III. Results and Discussion, IV. Conclusions, V. References, VII. Bibliography, VI. Appendix. The tables and figures are numbered in Roman and Arabic numerals respectively.

In this investigation, several new direct compression matrices produced by California and Hawaiian Sugar Company were evaluated. These matrices are refered to as C & H AI, AII, B, C, or Brown. The Roman numeral next to a letter code indicates that the product is prepared by the same process as the other product bearing the same letter code; only differing in the physical characteristics. The commercially available direct compression sugars studied are: DiPac, NuTab, and Emdex. These are trade names of Amstar Corporation, Ingredient Technology Corporation, and Edward Mendell Company respectively.

In some instances, the figures in this manuscript depict plots of the relationship between two parameters for up to six matrices. Therefore, for purposes of visual clearity, both solid and dotted lines have been used. The dotted lines do not differ in any manner from the solid lines. In both cases, no mathematical or empirical relationships are implied; the lines are the result of the joining of the data points.

PUBLICATIONS AND PRESENTATIONS

Based on the work presented in this manuscript, the following papers were published or presented at a national meeting.

PUBLICATIONS

1. Comparative evaluation of several direct compression sugars, Drug Development and Industrial Pharmacy 9, 8 (1983).
   Clive O. Ondari, Chester E. Kean, and C. T. Rhodes
2. Effects of short term moderate storage stress on the disintegration and dissolution of four types of compressed tablets Pharmaceutics Acta Helvetiae, 5, 149 (1984).
   Clive O. Ondari, Vadlamani K. Prasad, Vinod P. Shah, and C. T. Rhodes

PRESENTATIONS

1. Comparative evaluation of tne acid neutralizing efficiency of several direct compression antacid formulations, presented at the A.Ph.A. Academy of Pharmaceutical Sciences meeting, Miami Beach, Florida, November 1983. Clive O. Ondari, Chester E. Kean, and C. T. Rhodes.
2. Comparative evaluation of several direct compression sugars II, presented at the A.Ph.A. annual meeting, Montreal, Canada, May, 1984. Clive O. Ondari, Chester E. Kean, and C. T. Rhodes.

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I. INTRODUCTION

It is well recognized that the compressed tablet is the most widely used pharmaceutical dosage form in North America and Western Europe. Defined by the USP as "a solid dosage form containing medicinal substances with or without suitable diluent", tablets may be classified either as molded or compressed depending on the method of manufacture (1).

The formulation of tablets has undergone rapid change and development over the last several decades. With the emergency of precompression induced die feeding, high speed (and most recently, ultra-high speed) computer controlled presses, the manufacture of tablets has become one of the most sophisticated aspects of pharmaceutical production. In addition to technological advances, recent government regulations regarding the bioavailability and efficacy of pharmaceutical products have also played a major role in the advancement of tablet production.

Tablet design and formulation as it exists today can be thought of as "the process whereby the formulator ensures that the correct amount of the drug, in the right form, is delivered at or over the proper time at the proper rate and in the desired location, while having its chemical integrity protected to that point (2).

Tablet presses operate at varying speeds, ranging from less than a thousand to almost a million tablets per hour. In order to ensure that adequate weight uniformity is maintained, it is important, especially on high speed presses, that the material to be compressed possess acceptable flow characteristics. For smooth operation of the tablet press, the granulation or direct compression mix must have good compressibility and lubricant properties. Many of the active ingredients and excipients do not meet these criteria, and it is therefore necessary to prepare a suit-

able granulation prior to the compression process. Alternatively, a direct compression technique may be employed provided that the components meet the above mentioned criteria. A third method, dry granulation, is limited to situations where neither wet granulation nor direct compression can be used.

A. Some aspects of tablet manufacture

1. Methods of manufacture

a. Wet granulation

In spite of its costly nature, requiring intensive labor, considerable material handling, and costly equipment, wet granulation continues to be the most widely used process for tablet manufacture. Although many of the products currently being formulated by wet granulation could be made by direct compression, existing government regulations would define such changes as major modifications. These modifications would require changes in ingredients, or at least, changes in forms of previously used excipients. Hence, the newly formulated products would have to undergo additional stability, bioavailability, safety studies, and a new submission to regulatory agencies such as the FDA.

Additionally, wet granulation offers several advantages over direct compression. These advantages include: ease of attainment of acceptables content uniformity (particularly with soluble, low dosage drugs), ability to regulate moisture content of the granulation during the drying cycle, modification of flow characteristics by controlled particle size distribution, and good distribution of color additives. Through proper selection of granulation solution and the binder, the dissolution rate of a hydrophobic drug may be improved.

Wet granulation is not without its limitations. The primary limitation

is the high cost associated with the process in terms of labor, time, equipment, energy, and space requirements. Other limitations include soluble dye migration during the drying cycle, and a high incidence of component incompatability as a result of the close contact brought about by the use of the granulating solvent. In addition, heat and moisture sensitive drugs often can not be processed by this method.

b. Direct compression

Direct compression is the simplest tablet production method. In this process, tablets are compressed directly from powder blends of active ingredients and suitable excipients (including, disintegrants, and lubricants). These blends flow uniformly into the die cavities to form the compacts. The method offers several advantages over wet granulation. First and foremost, the process is economical; a limited number of processing steps are involved in direct compression compared to wet granulation. Other manufacturing variables such as the mode of addition of the binder, drying time, etc. are limited. In tablets made from direct compression the particles do not exist in agglomerate form (granules). Hence, upon contact with dissolution medium, a prime particle dissociation is affected. This in turn may result in faster dissolution which may indeed be the single most important factor controlling product bioavailability (3). Since no moisture is involved in the preparation of the blends for direct compression, the tablets made from this process tend to be more stable than those produced by wet granulation (4).

However, direct compression has several disadvantages. Many active ingredients have poor flow and compression characteristics. This generally requires that the active ingredient be incorporated into a matrix or a mixture of matrices to achieve adequate flow and compressibility. Sev-

eral advances have been made in modifying the particle shape and form of some active ingredients and fillers to render them more suitable for direct compression processing. Such success has been achieved with aspirin, acetaminophen, and several vitamins. However, these modifications tend to increase the price of the raw material, thus negating the cost advantage of direct compression.

In most cases, the amount of active ingredient(s) that can be incorporated into a matrix (dilution potential) is quite limited (usually less than 30%). Although this level varies with different active ingredients and matrix systems, it is a major limitation when formulating high dosage drug products. On the other hand, adequate distribution is sometimes difficult to achieve when working with low dosage drugs. Also, because of lack of, or low levels of moisture in direct compression blends, development of static charges may lead to unblending. This phenomenon can also occur as a result of vast differences in particle size or density among the components of the blends. The blends are most susceptible to unblending particularly in the hopper or feed frame of the tablet press. Another limitation of this method is the difficulty of achieving deep and uniform color distribution in tablets.

c. Dry granulation (Precompression or Slugging)

Dry granulation is the process whereby granules of powder blends are obtained without the use of heat or solvent. This method is usually reserved for those formulations which cannot be processed by either wet granulation or direct compression due to technical or economical reasons. The process entails the formation of slugs from the active ingredient and one or more excipient(s). These slugs are then milled and screened into a desired particle size distribution range. The "granules" are then mix-

ed with the remaining components of the formulation to obtain the final production blends.

2. Formulation of chewable tablets

Chewable tablets do not constitute a major portion of the pharmaceutical dosage forms. However, they offer unique convenience to young children and some geriatric patients who find swallowing difficult. Chewable tablets also provide a rapid onset of activity, such as in the treatment of hyperacidity conditions. They are also useful as target oriented dosage forms for the treatment of mouth or throat conditions.

In the production of chewable tablets, several formulation factors are taken into consideration. These factors include: the amount of active substance per tablet, flow characteristics of the production blend, compressibility, overall stability of the formulation, and organoleptic properties. Among these factors, organoleptic properties of the active ingredient(s) is perhaps the most important consideration for some formulations. It is generally accepted that, as the required amount of the active substance per tablet gets smaller and less bad-tasting, the task of achieving an acceptable formulation becomes easier (5). This is because of the variety of options available in attaining such a formulation. However, formulating an extremely bad-tasting or high dosage drug into a chewable tablet provides an enormous and difficult task. The final formula should be one with good taste, acceptable mouth-feel, bioavailability, stability, and quality. Additionally, the product should be prepared from an economical formula to ensure market success.

In order to achieve a product with the foregoing attributes, several formulation techniques and approaches are available. To solve the problem of bad mouth-feel or after-taste, the formulator may choose to micro-

encapsulate the active ingredient(s). This is a method of coating the drug particles or liquid droplets with polymeric material, thus masking the undesirable taste and forming relatively free flowing microcapsules. The particle size of the micro-capsules rangcs from 5 to 500 microns. The technique of micro-encapsulation is heavily limited by patents. A detailed review of the various methods of micro-encapsulation has been presented by Luzzi (6). Among the various methods described in the literature (7, 8), phase separation and coacervation appear to be the most suitable for taste masking. The polymers used in coating the core material include compounds such as carboxymethylcellulose, cellulose acetate phthalate, ethylcellulose, gelatin, polyvinylalcohol, gelatin-acacia, shellac, and some waxes. Through the use of coagulable water soluble egg albumin, Farhadieh (9) has patented an erythromycin form which is suitable for chewable tablet formulation. In addition to masking unpleasant taste, micro-encapsulation may eliminate or minimize potential incompatibility problems. Such success has been reported by Bakan and Sloan in the formulation of aspirin and chlorpheniramine maleate (10). It may be noteworthy that upon compression, the microcapsule integrity may be partially or completely compromised. This, in combination with the extent to which the tablet is chewed, and the length of time the drug remains in the mouth may determine the degree of taste-masking.

Adsorption of an active ingredient (with objectionable mouth-feel) onto a substrate capable of maintaining the adsorption while the tablet material is in the mouth may be an alternative method of masking undesirable taste. In this case, the release of the active ingredient from the substrate is pH dependent, and occurs in the stomach or in the intestinal tract. A commercially available adsorbate is that of dextromethorphan

adsorbed onto magnesium trisilicate by Roche (11). This product is available in a micronized powder with an active drug content of 10% (w/w). It is possible to form adsorbates from other materials such as Veegum and silica gel. This process requires that a drug be dissolved in a solvent, mixed with the substrate, and the solvent evaporated leaving drug adsorbed upon the substrate (5).

Ionic exchange, a method analogous to adsorption, has been used not only to mask taste, but also to enhance product stability. In this method, a substrate resin (ionic in nature) cationic or anionic, possessing an affinity for oppositely charged ions on the drug molecule is used. As in adsorption, the ideal complex is one in which the drug-resin complex remains intact under the salivary pH conditions, but capable of dissociating in the intestinal environment. Such a complex involving a cationic resin, Amberlite (substrate) and vitamin B_{12} is commercially available from Roche as Stablets (11). As alluded to earlier, this complexation also enhances product stability. The resin-bound form of vitamin B_{12} is more stable in the presence of the acidic vitamin C (a common combination in chewable multivitamin tablets).

The most widely used techniques for taste masking and stability improvement are spray congealing and spray coating. In spray congealing, particles are suspended in a molten coating material which is then pumped into a spray dryer in which cold air is circulated. The droplets congeal upon contact with the cold air and are then collected as free flowing particles. On the other hand, spray coating entails the evaporation of the solvent from the solution of the coating material. This leaves a film of coating material on the particles being coated. These two techniques produce spherical particles which are usually better flowing than the

original form. Sodium dicloxacillin and tetracycline have been successfully spray coated to yield free-flowing products suitable for incorporation into chewable formulations (12). These products are coated with a mixture of ethylcellulose and sparmaceti dissolved in methylene chloride.

The formation of different salts of derivatives of a drug may be an alternative method of circumventing an unpleasant taste. However, this approach has legal limitations in that it creates a "new" drug entity. Thus, subject to safety, efficacy, and stability testing as required in the Investigational New Drug (IND) and New Drug Application (NDA) guidelines of the FDA.

The traditional method of wet granulation also offers an approach of masking unpleasant taste in a chewable formulation. A bad tasting drug is granulated with or without excipients with the aid of a binding solution. This method however, requires higher concentrations of binder material (compared to formulation of non-chewable formulations) to ensure adequate coating. The conventional binder materials such as povidone, cellulose derivatives, polyethylene glycols, gelatin, acacia mucilage, and corn paste are used. It is recommended that where possible, the drug be granulated with a sweet binder, and an intra-granular disintegrant (5). The latter ensures that the granules disintegrate in the gastrointestinal tract following mastication. The general limitations of wet granulation discussed in Section Ia also apply to this method.

A technique that has been used successfully to counteract the unpleasant taste of penicillin is the use of amino acids and protein hydrolysates (13). Some of the preferred amino acids are: sarcosine, alanine, taurine, glutamic acid, and glycine (5). Among these amino acids, glycine is probably the most widely used.

a. Flavoring of chewable tablets

Since a majority of the chewable tablet formulations, are available as over-the-counter products, flavor and appearance can make the difference between commerical success or failure of a product.

The trend in the pharmaceutical industry today is shifting from the traditional usage of flavors such as mint, wintergreen, clove, eucalyptus, lemon, and orange just to render the product palatable. Todays flavoring encompasses a variety of attributes such as initial impact, mouth-feel, after-effects, and olfactory sensations. These considerations are made in an effort to produce a tablet with good taste and not merely to mask a bad taste. Some of the technology of pharmaceutical flavoring is borrowed from the food industry where a considerable amount of research work has been done (14-16). The selection of the appropriate flavor in the pharmaceutical industry today is a well-researched, and executed process. The establishment of flavoring criteria and approach is carefully considered. A typical, well constructed flavoring plan would be one which firstly involves a general evaluation of the active ingredient(s) with regard to: basic taste, inherent flavor or aroma, intensity of these three properties, mouth-feel, taste test, and overall impression. Should taste-masking be necessary, the second step would be the selection of an appropriate method (discussed in Section 2). The third step involves the selection of the other formulation components (eg., vehicles, lubricants, colors, etc.).

In order to create a "baseline" for objective evaluation of the tablet formulation, unflavored tablets are prepared. The "baseline" batches are then comparatively evaluated against flavored batches. Some general guidelines for flavor selection exist for those cases where it is not feasable to carry out elaborate trials. By considering the formulation

under the following categories: therapeutic classification e.g. antacid, multivitamin, etc.; active drug, in terms of structure, incompatabilities, pH versus stability, taste and mouth-feel evaluation, dose per tablet and frequency of administration; intended patient population; and marketing preference, i.e. prescription versus over the counter, a formulator can select preliminary flavors with relative ease (17). When the final flavor is selected, it is important to establish the optimum level, although concentrations of 0.1 to 3% (w/w) are generally recommended. The level of flavors in chewable tablet formulations is especially critical since these compounds have been implicated in behavior modifications in children (18, 19).

The incorporation of flavors into formulation mixtures generally involves blending of the flavor powder into the final blend, usually just prior to the addition of the lubricant. If several flavored base-line formulations are prepared, taste panels may be used to determine which production is finally presented to the market. However, the in-put of marketing personnel cannot be over-emphasized.

As indicated in the discussion above, the aesthetic nature of a product may actually make a total difference between commercial success or failure of a chewable product. It is therefore important that the tablet product contain the most suitable color. Although the same general considerations of color usage in regular (swallowed) tablets apply to chewable forms, there are significant differences in the criteria for selection. The choice of color or color combinations should be in agreement with the selected flavor. The use of colorants in pharmaceutical products has been controlled in the United States since the enactment of Food and Drug Act of 1906. In this act, the Depart-

ment of Agriculture established a group of "permitted colors". Colors from this group may be used in foods, drugs, and cosmetics after certification by the Food and Drug Administration. The certification ensures that the colors meet the required specifications, hence, certified dyes and lakes. Various colors may be created through manipulation of the original "permitted colors" to create new colors. However, these blends must be recertified (20). Under the Act, the certified colors are classified into three groups; FD&C dyes which may legally be used in foods, drugs, and cosmetics; D & C dyes which may legally be used in drugs and cosmetics; and external D & C dyes which may legally be used only in externally applied drugs and cosmetics. The use status of certified colors is regulated by the Food and Drug Administration which may make changes whenever necessary. Such changes and current status are published in the Federal Register. A comprehensive list of colors and their matching flavors has been given by Daruwala (5).

3. Direct compression excipients

Due to special flow and compression requirements of direct compression, only a few matrices are suitable for the process. An extensive list of the properties of an ideal direct compression excipient has been given by Khan and Rhodes (21). Some of the most widely used direct compression excipients (matrices) include several forms of lactose, starch, microcrystalline cellulose, dicalcium phosphate, and sucrose. A detailed descrption of each of these matrices is given below.

a. Lactose

Available in a spray-dried form, lactose is the earliest and the most widely used direct compression matrix. The wide availability of this material from several sources makes it an attractive product. Initial

results with spray-dried lactose were disappointing due to browning (22). This reaction is catalyzed by tartrate, citrate, and acetate ions (23).

Advances in the spray-drying technique have eliminated the extent of browning considerably. Spray-dried lactose which has about 5% moisture content has less than satisfactory compressibility. However, studies have shown that tablets made from this material are not significantly affected by elevated temperature, high humidity or sunlight (24). The product's (lactose) poor compressibility and low dilution potential prompted further research for a more versatile form of lactose. "Fast-Flo" Lactose is a product of such efforts. Through process modification which inhibit the growth of microcrystals, α-lactose monohydrate microcrystals are held together in spheres. This configuration affords the product excellent fluidity, low hygroscopicity, and high compressibility.

Lactose is also available in an anhydrous form, without the water of hydration. Because of the high amounts of fines, this product has less than optimum flowability. This form may pick up moisture under high humidity conditions resulting in an increase in tablet volume of up to 15% (3).

b. Starch

In its natural state, starch lacks the compressibility and flowability essential for a direct compression matrix. The modification that has received considerable industrial acceptance is that of Sta-Rx-1500. This is a partially hydrolyzed starch that has better flow properties than Starch USP. Although Sta-Rx-1500 can be compressed into tablets (25, 26), its major application is as a disintegrant (27).

c. Microcrystalline cellulose

This form of cellulose was introduced as a direct compression matrix

in the early 1960's following the isolation of cellulose fiber chains. Under the trade name Avicel, microcrystalline cellulose is available in several grades, differing in particle size and flow characteristics. Due to the presence of hydrogen bonding among the product's particles, excellent compressibility and high capacity can be achieved. Other favorable properties of this product include low bulk density, broad particle size range, and low coefficient of friction. Several studies concerning the use of microcrystalline cellulose in tableting have been reported in the literature (28-39). Khan and Rhodes have shown that formulations containing microcrystalline cellulose have pressure sensitive disintegration (40). Due to cost considerations, this product is seldom used as the sole matrix in a direct compression formulation.

d. Dicalcium phosphate

Dicalcium phosphate dihydrate, an inorganic product, is available in an agglomerated form under the trade name Emcompress from Edward Mendell Company. Its excellent flow and compressibility make it very suitable for use in high speed tablet presses. This product is relatively inexpensive, and possesses an acceptable degree of physical and chemical stability. Studies have shown that the material will lose water of hydration at elevated temperatures resulting in surface hardening (22). Due to the product's poor solubility in neutral or alkaline media, its use in the formulation of low water soluble and alkaline sensitive drugs is limited. Accelerated stability studies have shown that this product is unstable in formulations containing acidic compounds, ascorbic acid and thiamine hydrochloride (41). Khan and Rhodes have investigated the effect of compressional force on the disintegration time (42) and dis-

solution efficiency (43) of dicalcium phosphate dihydrate formulations containing soluble and insoluble disintegrants. Rhodes and co-workers have reported the effect of various stress conditions on the physical properties of dicalcium phosphate dihydrate formulations (44).

e. Sucrose

Sucrose in its raw form has poor flow, although it can be compressed into a solid mass. The lack of adequate flow has necessitated modifications to render the product adaptable to tablet production by direct compression. The material's universal availability and abundance has led to recent depression in its world market prices. The depression in sugar prices has in turn led to an intensive effort to find new methods of using the product.

Successful modification of the basic sucrose crystals is exemplified by DiPac and NuTab. These are co-crystallized products consisting of 97% sucrose with 3% modified dextrins, and processed sucrose with 4% invert sugar; 0.1 to 0.2% corn starch, and magnesium stearate respectively (45, 46). It may be noteworthy that the process of sugar refining involves five basic unit operations, namely centrifugation, filtration, decolorization, evaporation, and crystallization. The crystallization unit operation is manipulated to result in a new crystal aggregate which has enhanced tableting properties. In the formulation of DiPac, the resulting co-crystallized material contains all of the solids of the original feed material. Individual grains of sucrose are agglomerated into microsized crystals (3 to 30 microns) with the additive ingredient (starch) being primarily located in the interstitial spaces between the sucrose crystals. It is thought that the DiPac agglomerate have a 'lacy' porous cluster of very small individual syrup coated crystals bonded together at their

interface by points of contact. It is this porous nature that provides co-crystallized products with their tableting characteristics (47). The essential steps involved in the patented process of manufacturing DiPac are illustrated in Appendix 1.

4. The use of Tablet Presses in Powder Characterization

Instrumented tablet presses have been in use in the pharmaceutical industry for about three decades. The use of these instruments in the industry represents part of a continuing effort to convert tablet production from an emperical state into a systematic, and scientifically quantifiable process. Studies of tablet press instrumentation have encompassed both basic research, and the physics of tablet production. However, those studies involved with the application of this technology in analyzing the compression characteristics of individual ingredients, the effect of additives, lubricant effects, total formulation, and scale-up procedures are of considerable practical value (50-57).

In order to understand how instrumented tablet presses can be of value to a pharmaceutical researcher, an understanding of the process of manufacturing tablets by compaction is essential. The production of tablets involves the compaction of a powder system with an external force. The powder is contained, and confined within the die cavity and the force is applied through the punches (upper and lower). The compression of the powder by the punches consolidates the powder material while displacing air from the void spaces. When force is applied to the powder in the die(s), bulk volume decreases through a number of mechanisms. These mechanisms include: repackaging of the particles, elastic deformation (a reversable process), plastic deformation and or brittle fracture (when the elastic limit of the system is exceeded), and further

compression.

The instrumentation of tablet presses is an attempt to measure the applied force. A commonly used instrument to determine such a quantity is the transducer. The transducers used in tablet presses are those that convert force measurements to electrical signals in the form of voltage. The two types of force measuring devices currently used are the strain gauges and piezoelectric transducers. A strain gauge consists of a coil of high resistance wire mounted on a paper backing. This gauge shows a change in electrical resistance in direct proporation to its change in length. Piezoelectric transducers contain quartz crystals which develop electrical charges proportional to the applied force. Strain gauges may be bonded to the punches or any other part of the press subject to similar changes. During compression, the applied force produces a small elastic deformation in the punches. This deformation in turn produces a change in the resistance of the strain gauges.

Piezoelectric transducers are available in many sizes, and may be placed in several locations of the tablet press. However, piezoelectric transducers offer the advantages of being less sensitive to temperature effects, and require no bonding to the tablet press. The major limitation of this type of transducers is that the change developed in them (as a result of applied force) dissipates over time, and thus are not useful in static measurements.

The signals produced during the various cycles of the tablet press may be recorded by various devices such as oscilloscopes, recording oscillographs, and high speed chart recorders. The measurements recorded during a given run are compared to some standard or expected patterns, and may be used to control a particular phase of the tableting process.

Schwartz has described how instrumented tablet press data can be used as 'finger-prints' of tableting ingredients (58).

Whether a formulator uses a single punch or rotary instrumented tablet press, the data generated allows one to see how variables, such as specific surface area, apparent density, porosity, hardness (crushing strength), volume, thickness, disintegration time, dissolution, lower-punch force, ejection force, etc., relate to compressional force. This information would indicate the force required to produce acceptable tablets. It would also be valuable in assessing how various tablet properties vary with different pressure levels, reproducibility of the process in use, materials' batch to batch variability and scale-up.

In order to facilitate rapid data collection on a large number of tablets, and to determine various compression profile parameters, instrumented tablet presses are interfaced with computers. The vast amount of data collected enables the generation of the entire compression profile. Such profiles can provide a useful tool for trouble-shooting work.

Although a considerable amount of data has been generated with the use of instrumented tablet presses, there is no apparent uniform approach in its interpretation. Krycer and Pope (59) have demonstrated the existence of many discrepancies in the literature. These authors have also observed that there are serious conflicts in the conclusions drawn by researchers that employ similar methods. Nevertheless, recognizing that during tablet compression, the powder particles will undergo plastic deformation and/or brittle fracture before a compact is formed, the relative proportions of these changes in a formulation may be evaluated with the aid of 'Heckel plots' (60). The log of $^{1}/(1-d)$, where d is the relative density of the compact, is plotted as a function of

applied pressure. Heckel plots generated for variously sized fractions of a given material become superimposed when brittle fracture is the major effect due to the rapid destruction of the original particle size. These curves however, remain discrete when plastic deformation is the predominant process. The radial force (force transmitted radially to the die wall) to applied force profiles are also useful in assessing plastic deformation and brittle fracture. Lubricating properties are evaluated by measuring the residual force between the die wall and the tablet. The generation of applied force versus punch displacement curves enables the calculation of the work involved in the tableting process. This technique has been applied to evaluate lubricating efficiency (61, 62).

5. Tablet Coating

A non-chewable tablet formulation may be coated because of difficulty in overcoming unpleasant taste and odor, decomposition of the active ingredient(s) due to environmental exposure (particularly for hygroscopic formulations, such as those made from sugar matrices), to increase aesthetic appearance of the product, or to eliminate undesired effects of the active ingredient in the stomach.

Tablet coating can be divided into four basic categories sugar coating, film coating (non-enteric and enteric), compression coating, and other new concepts (4). The choice of one method over the others will depend on specific pharmaceutical or medical considerations. The basic processes used in the application of the coating are pan coating, air suspension coating, dip coating, and compression coating. Currently, pan coating is the most widely used method in industry. Due to technical and economical limitations, compression coating and dip coating have not gained significant industrial acceptance.

a. Sugar coating

Sugar coating is one of the oldest processes in the pharmaceutical industry. The technique has remained more of an art than a scientific process because of the secretive nature with which it is carried out. However, several modifications have been suggested to improve the overall process (63). Among the modifications, only pan-spraying technique has received considerable acceptance in industry. Some of the significant improvements that have been made (over the original process) include: atomizing systems to more evenly distribute coating solutions, lakes of dyes to achieve uniform color with minimum color coats, and modern coating that can more efficiently dry the tablets between coats. The process is basically carried out in five stages: (i) sealing-imparts a sufficient degree of water proofing to prevent inward penetration of moisture, (ii) sub-coating, achieves rapid build up and rounds of the edges, (iii) smoothing-converts the deficiencies of the subcoating stage (iv) coloring-enables product identification and makes the product elegant, and (v) polishing-the finishing touch. A comprehensive review of the process of sugar coating, and some of its improvements has been made by Sutaria (64).

It is apparent that two factors threaten the utility of sugar coating in the pharmaceutical industry. First, the difficulty of automation of the process has severely limited its expansion (65, 66). Second, only very few skilled individuals are able to perform the technique adequately. The stability of sugar coated tablets has been shown to be less than satisfactory (67). In some instances, this may be due to cracking of the coating as the tablet changes shape with variations in environmental conditions, or when water migrates into the core. However, in some cases,

the coating may harden considerably (without cracking), thereby impeding prompt disintegration of the tablet core.

b. Film coating

Film coating is a relatively new technique compared to sugar coating. The first commercial (non-enteric) film coated product was introduced onto the market in 1954 (2). Film coating may be divided into two categories, namely enteric film coating and non-enteric; depending on the solubility of the coating material in gastrointestinal fluids.

The rapid development of this process may be attributed to the vast interest not only in its pharmaceutical application, but also in other areas where surface coating is of concern. A number of considerations have been cited as advantages of film coating over sugar coating. These advantages include the reduction of coating time and material; lack of significant increase in tablet weight; no undercoat or water-proof coat required; durability and resistance to chipping and cracking; tablet can be monogrammed for identification; effective protection to light, air, and moisture; lack of adverse effects on disintegration time; non-aqeous coating solutions can be used; and feasibility of standardization of the process and materials.

Materials such as waxes (68), shellac (69), cellulose derivatives (70) and polymeric compounds soluble in, or permeable to gastrointestinal juices have been used for film coating. Hydroxypropyl methylcellulose (71) methyl hydroxyethylcellulose, ethyl cellulose, hydroxypropyl cellulose, povidone (72), sodium carboxymethyl cellulose, and polyethylene glycols (73) are the most widely used polymers.

In contrast to non-enteric film coating, enteric coating has been in existence for quite a long time (74). Enteric coating protects acid

labile drugs from gastric fluids. It also protects gastric mucosa from irritating compounds. Courveur and co-workers (75), and Kanig (76), have described an ideal enteric coating material as one that is impermeable to gastric juices, susceptible to intestinal juices, non-reactive, stable during storage, provides a continuous coating, non-toxic, inexpensive, and easy to apply with minimum equipment.

Although the USP XX has disintegration specifications, and USP XXI will contain both disintegration and dissolution specifications for enteric coated tablets, these products will continue to be troublesome. Studies have shown that even for those samples that pass in-vitro tests, successful in-vivo performance can not be assured (75, 78, 79). This variability in performance is, at least in part, due to inter, and intra-subject gastric and intestinal pH variations.

Among the vast number of materials that have been evaluated or used for enteric coating, the most commonly used products are shellac and its cellulose acetate phthalate derivative (78). Studies have shown the superiority of cellulose acetate as an enteric coating product (80, 81). However, high hygroscopicity, susceptibility to hydrolytic breakdown upon storage, and permeability to ionic solutions are the major limitations of this material (76). Other materials that have been successfully used recently are: copolymers of maleic anhydride and ethylene compounds (82), and ionic polymers synthesized from methacrylic acid and methacrylic esters (83).

The selection of the solvent for use in film coating as undergone dramatic changes in the last decade with more stringent environmental regulations through the Environmental Protection Agency (EPA) and Occupational Safety Hazard Administration (OSHA). The use of organic solvents

such as methanol, chloroform, acetone, methylene chloride has been significantly reduced (84). The high cost of petroleum products has also played a significant role in the reduction of the use of organic solvents in film coating. Water-based colloidal coating dispersion systems, eg. Aquacoat (30% ethyl cellulose pseudolatex) are gaining popularity.

d. Compression coating

This method basically involves the compression of preformed coatings onto tablet cores. The technique has been made possible by the development of sophisticated compression machinery. However, with the advent of film coating, compression coating is rarely employed in the manufacture of new drug products.

B. Evaluation of tablets

Tablet properties can be divided into two categories: those listed in the official compendia, and those widely evaluated by the manufacturers. The official tests include tablet weight variation, assay for active ingredient(s), content uniformity, disintegration, and dissolution. Descriptions of these tests are available in compendia such as the United States Pharmacopiae (1), and the British Pharmacopiae (85). The first three official tests listed above ensure that an adequate amount of a drug is delivered to the body. Disintegration time and dissolution are in-vitro indicators of the in-vivo release patterns of the dosage form. These two parameters are often dependent on tablet hardness. In the evaluation of antacid tablets, acid neutralizing rates and acid neutralizing capacity (efficiency) are used in place of dissolution rates (86-89). Some studies have shown a correlation between disintegration time and physiological activity (90,91). However, other studies have

shown that such a correlation does not exist (92). In recent years more emphasis has been placed on dissolution as the better in-vivo performance indicator. The correlation between dissolution rate and drug absorption has been documented (93-95). Tests such as tablet thickness, hardness, friability, and resistance to impact stress are unofficial. Variability in tablet thickness is often indicative of inadequate flow characteristics of a formulation. The other unofficial tests are indicators of the ability of a formulation to maintain its integrity during packaging, shipping, and patient handling.

B. Accelerated stability testing

The single major purpose of accelerated stability testing is to permit one to predict the shelf life of a product at some label storage condition, usually "room temperature". While kinetic evaluation of stability data may be of value in most dosage forms, this approach is limited when applied to tablets. Due to the multiplicity of excipients in tablet formulations, the use of rate constants through Arrhenius equation is impractical. Several approaches have been used to investigate the stability of pharmaceutical tablets. Chafetz has suggested the use of stability indicating assays (96). These are procedures which afford the selective determination of a drug substance in the presence of its decomposition and reaction products. Interactions between ingredients in a solid dosage form may lead to changes in physical properties such as equilibrium solubilities, partition coefficients, and dissolution. Guillory and co-workers (97) have suggested control procedures to identify such interaction through the use of differential thermal analysis (98). Diffuse reflectance has also been shown to be of value in solid-solid interaction studies (98). This technique enables the determination of chemi-sorption

due to surface chelation.

The literature reveals several publications of an empirical or practical nature describing incompatabilities, instabilities or other changes in the solid state (99-109). In these studies, changes in parameters (non-chemical) as a function of time are reported. The moisture sorption and volume expansion of tablets made from various forms of lactose has been reported by Otuska and co-workers (110). The moisture sorption and tablet expansion was shown to occur more readily with α - lactose leading to the formation of the monohydrate.

The effect of the container on the stability of pharmaceutical products is of considerable importance. Inter-tablet migration, a phenomenon which involves capillary condensation, exemplifies the importance of containers in product stability (111). The influence of environmental conditions on tablet properties is perhaps the most widely investigated area of tablet stability. The effect of light on color stability of tablet formulations has been reported (112-114). Alans and Parrott (115) have shown a relationship between the changes occurring in the dissolution rate of hydrochlorothiazide tablets at elevated temperature and those occurring after prolonged storage at room temperature. The decrease in the dissolution rates of sodium salicylate (116), and acetominophen (94) tablets due to aging has been shown. A study on phenylbutazone tablets showed a gradual decrease in the dissolution rate with aging (94). Other valuable studies on the effect of aging on the physical properties of tablets include those of Rhodes and co-workers (117-120), Lachman (121), and Sangekar et al (122).

C. Objectives and Significance of the Study

Although the production of tablets by direct compression has been used successfully for a number of years, the understanding of the process is still based substantially on empiricism. In particular, little has been done to rationalize the use of sugars as direct compression matrices. Secondly, little consideration has been given to the effect of cyclic environmental changes on the stability of pharmaceutical products.

The prime objective of this study was to evaluate comparatively the potential utility of several new direct compression sugar matrices. Additionally, the effects of cyclic environmental changes on some fundamental physical properties of compressed tablets have been investigated.

This study provides a rational approach to tablet formulation evaluation and stability analysis. The study is of both theoretical and practical importance not only to the pharmaceutical industry, but also to the food and chemical industries where packaging of raw materials and finished products is of paramount concern.

II. EXPERIMENTAL

A. Materials

1. Formulation components

Sodium ascorbate AG (Lot # 112101)[1]

Ascorbic acid 90% (Lot # 019061)[2]

Microcrystalline cellulose (Lot # 3838-87)[3]

F D & C Yellow # 6 (Lot # AC0693)[4]

Micronized silica gel (Lot # 52003)[5]

Orange flavor (Lot # L12281)[6]

Stearic acid (Lot # G19925K08)[7]

Magnesium stearate (Lot # 793404)[8]

Niacinamide (Lot # 548112)[9]

Pyridoxine (Lot # 840031)[10]

Riboflavin (Lot # 358030)[11]

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[1]Hoffman La-Roche, Nutley, New Jersey.

[2]Hoffman La-Roche, Nutley, New Jersey.

[3]FMC Corporation, Newark, Delaware.

[4]Warner Jenkinson, St. Louis, Missouri.

[5]Davidson Chemical, Baltimore, Maryland.

[6]Warner Jenkinson, St. Louis, Missouri.

[7]Ruger Chemical Company, Irvington, New Jersey.

[8]Fisher Scientific Company, Fairlawn, New Jersey.

[9]Hoffman La-Roche, Nutley, New Jersey.

[10]Hoffman La-Roche, Nutley, New Jersey.

[11]Hoffman La-Roche, Nutley, New Jersey.

Chlorpheniramine maleate (Lot # D14539K01)[12]

Phenylpropranolamine hydrochloride (Lot # F14727H31)[13]

Dextromethorphan hydrobromide (Lot # 3011922)[14]

Pseudoephedrine hydrochloride (Lot # G1950FG10)[15]

Aluminum hydroxide/magnesium carbonate gel (Lot # 16599)[16]

Micronized silica gel (Lot # 78 5004)[17]

Peppermint flavor (Lot # S-29702)[18]

Calcium carbonate (Lot # P2352CC)[19]

Pectin (Lot # F15852K16)[20]

Aluminum hydroxide gel (Lot # D18025C14)[21]

C&H A, C&H B, C&H C, C&H Brown Sugar (Experimental Lots)[22]

DiPac (Lot # 31E)[23]

NuTab (Lot # T-JD917M)[24]

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[12]Ruger Chemical Company, Irvington, New Jersey.

[13]Ruger Chemical Company, Irvington, New Jersey.

[14]Hoffman La-Roche, Nutley, New Jersey.

[15]Ruger Chemical Company, Irvington, New Jersey.

[16]Reheis Chemical Company, Berkeley Heights, New Jersey.

[17]Davidson Chemical Company, Baltimore, Maryland.

[18]Food Materials Corporation, Chicago, Illinois.

[19]Desmo Chemical Corporation, St. Louis, Missouri.

[20]Ruger Chemical Company, Irvington, New Jersey.

[21]Ruger Chemical Company, Irvington, New Jersey.

[22]California and Hawaiian Sugar Company, Crockett, California.

[23]Amstar Corporation, New York, New York.

[24]Ingredient Technology Corporation, Pennsauken, New Jersey.

B. Equipment

Engelsmann tapper[1]

Ohaus moisture balance[2]

Fisher shaker[3]

Analog balance[4]

Strip chart recorder[5]

Stainless steel hopper (from Stokes model F press)[6]

Scanning electron microscope[7]

Stokes model F tablet press (single punch)[8]

Computer (Model PDP-11)[9]

Computer - Apple (Model IIE)[10]

Mettler analytical balance (Model H-8, PR1200)[11]

Micrometer[12]

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[1]J. Engelsmann, A.G., Ludwishafen, West Germany.

[2]Ohaus Scale Corporation, Florham, New Jersey.

[3]Fisher Scientific Company, Fairlawn, New Jersey.

[4]Sartorius, West Germany.

[5]Linear Instruments Company, Dedham, Massachusetts.

[6]Stokes - Penwalt Company, Warminister, Pennsylvania.

[7]Cambridge Instruments, Cambridge, England.

[8]Stokes - Penwalt Company, Warminister, Pennsylvania.

[9]Digital Computer Company, Marlboro, Massachusetts.

[10]Apple Computer Company, Cuperton, California.

[11]Zeus Instruments Company, West Germany.

Erweka hardness tester (Model NR 19306)[13]

Tarbula Mixer[14]

Fitzmill[15]

Erweka friabilator[16]

USP disintegration apparatus[17]

USP paddle apparatus[18]

Perkin-Ellmer Hitachi spectrophotometer[19]

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[13]Erweka Apparatabau, Frankfurt, West Germany

[14]Tarbula Instruments, Switzerland

[15]W.J. Fitzpatrick Co., Chicago, IL

[16]Erweka Apparatabau, Frankfurt, West Germany

[17]Vandekamp, Van-kel Industries, Chatham, NJ

[18]Hanson Research Corporation, Northridge, CA

[19]Hitachi Instruments, Tokyo, Japan

[20]Corning Glass Works, Corning, NY

[21]Bechman Instruments , Fullerton, CA

2. Tablets evaluated in aging study

The following commercially available tablets were evaluated for the effects of aging as described in part 4 of section C:

sugar coated chlorpromazine 50 mg,[25]

film coated chlorpromazine 50 mg,[26]

enteric coated chlorpromazine 325 mg.[27]

prednisone 10 mg calibrator,[28]

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[25]Lot # 2050T76, Smith, Kline and French, Philadelphia, Pennsylvania.

[26]Lot # X-43177, Warner Lambert Company, Ann Abor, Michigan.

[27]Lot # 4AE38A, Eli Lilly Company, Indianapolis, Indiana.

[28]Dissolution test performance standard, National Center for Drug Analysis, St. Louis, Missouri.

C. METHODS

1. Intrinsic powder properties characterization

The following intrinsic properties of the matrices were determined: bulk and tap densities, moisture content (loss on drying), particle size distribution, and flow. Bulk volume was measured by pouring a 50g sample of powder into a 100 ml graduated cylinder from a height of approximately 2.5 cm. Three volume measurements were obtained for each matrix, and the values were averaged. Bulk density (gm/ml) was calculated as: weight (50g) divided by bulk volume (ml). Tap density was determined from the volume of 100g samples of powder subjected to a motorized tapping device[1] for 1000 cycles. Moisture content was determined by heating 10 gm samples of the bulk powders on an Ohaus moisture balance[2]. A nest of sieves, sizes (U.S. Standard) 20, 40, 60, 100, and 170, was used to measure the particle size distribution. The sieve stack was shaken for two minutes an a Fisher shaker[3]. Three replicate runs were performed for each matrix, and the cumulative weight percentage of powder at each seive level was calculated.

Unlubricated samples (one kilogram in size) of each matrix were evaluated for intrinsic flow properties by a recording flow meter as described by Rhodes et al (123). The flow meter consisted of an analog balance[4], a strip chart recorder[5], and a stainless steel hopper[6] suspended over the analog balance. A glass plate was used to close the opening of the hopper. The recorder was calibrated such that one kilogram of weight, when placed on the balance (tared with an aluminum pan), would cause the recording pen to deflect the entire scale. One kilogram of the material to be evaluated was placed in the hopper. When the glass plate was removed from the opening of the hopper, the powder fell on

the aluminum pan, causing the pen to respond in a manner characteristic of the powder system. The recorder was set to the record mode simultaneously with the removal of the glass plate. The falling weight was recorded as a function of time. The chart speed was kept constant at 30cm/minute. The pen tracings (flow grams) were then analyzed for linearity and mass flow (grams/second). The linearity term was calculated from the formula:

$$\text{Linearity} = (r^2 - 0.8) \times 100$$

where r^2 is the coefficient of determination. Three replicate flow grams were determined for each powder system. The values for mass flow and linearity were averaged.

Scanning electron micrographs of the matrices were obtained. The bulk powders were sprinkled evenly on adhesive - coated steel stubs. The samples were then coated with a 50/50 gold-palladium mixture. The coated stubs were placed in an electron microscope[7] and photographed by a Polaroid camera (located at the Graduate School of Oceanography, University of Rhode Island).

2. Formulation and evaluation of tablets made from sugar matrices

Several blends containing a matrix (C&H A, B, C, NuTab, and DiPac) and half a percent magnesium stearate were compressed into placebo tablets. An instrumented Stokes model F single punch press[8], located at Merck Sharp and Dohme's Research Laboratories, West Point, Pennsylvania, was used. The tablet press was instrumented with piezoelectric transducers and interfaced with a PDP-11 computer[9]. The software used with the computer enabled rapid collection of data concerning a large number of tablets. The computer facilitated the generation of several compression parameters. A transducer in the upper punch holder measured

applied force as a function of time. Transmitted and ejection forces were measured by a transducer in the lower punch holder. The computer generated force/time curves for applied and transmitted forces by receiving signals at a rate of 500 data points per second. In order to construct ejection force/time curves, the computer received 2000 data points per second. The following parameters were generated for applied and transmitted force curves: peak width (seconds, the duration of the compression event), center (seconds, time to reach the peak in the compression curve), maximum slope on the ascending curve (the maximum positive finite value for the change of force as a function of time, Newtons/second), inflection point on the ascending curve (time between start of the compression event and the time when positive change in force as a function of time is maximal, seconds), inflection point ordinate (the value of force, F, at the inflection (Newtons), and area (total area under the compression curve, Newtons seconds). A sketch of the compression parameters of an applied force curve is shown in Figure 1 Since the ejection curve is not as smooth as the compression curve, only the peak height was obtained for the ejection force curves.

Based on data from the above mentioned study, formulation work was carried out using the following matrices: C&H A, B, DiPac, and NuTab. A brown matrix manufactured by C&H was also included in this series. The formulas used to evaluate the formulation efficiency of the above matrices were: aspirin (pediatric), ascorbic acid, multivitamin (containing niacinamide, riboflavin, pyridoxine, and ascorbic acid), and antihistamine. The formulation mixtures were compressed into tablets by the use of an instrumented Stokes model F single punch press located at E.R. Squibb Institute for Medical Research, New Brunswick, New Jersey.

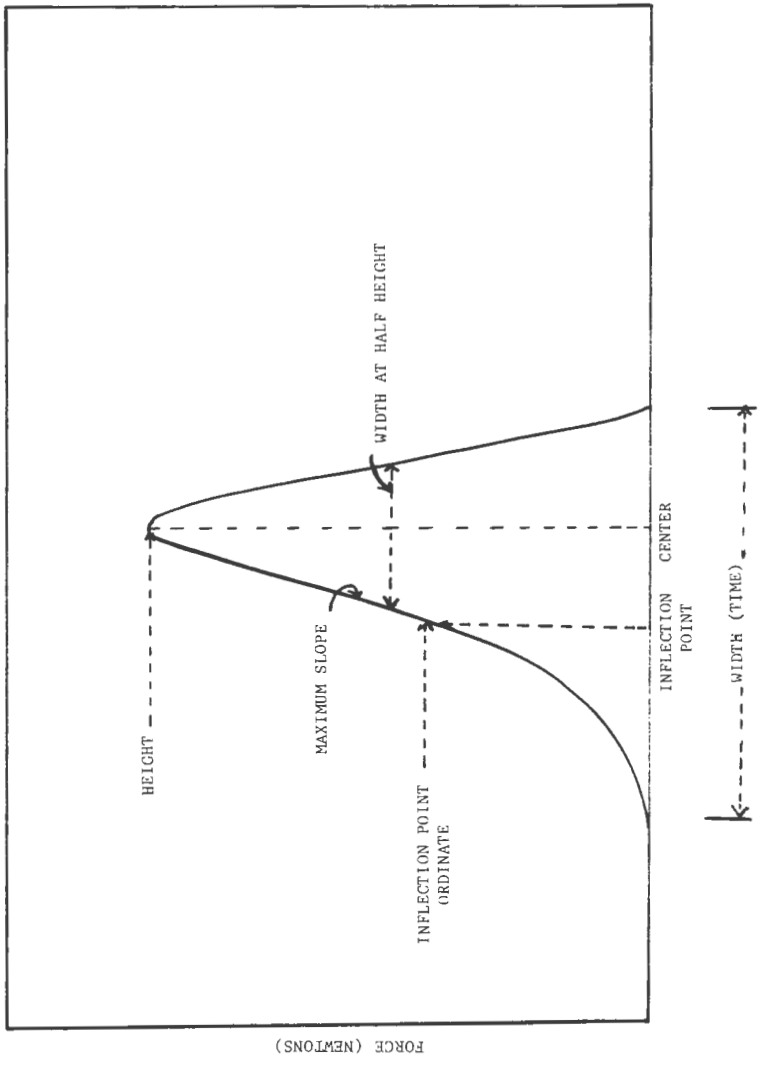

FORCE (NEWTONS)
HEIGHT
MAXIMUM SLOPE
INFLECTION POINT ORDINATE
WIDTH AT HALF HEIGHT
INFLECTION CENTER POINT
WIDTH (TIME)
COMPRESSION CURVE

FIGURE 1

The tablet press was instrumented with two piezoelectric transducers (one for each punch holder, upper and lower) and interfaced with an Apple IIE[10]. The software to this computer enabled the calculation of peak height (compression curve) by picking signals off the press at a rate of 200 data points per second. A mean of peak height from data on ten tablets was calculated. Since the lower transducer was non-functional, no ejection force parameters were measured. In addition to the tablets made on the instrumented tablet presses, antacid, antitussive, and antidiarrhea tablets were prepared on a non-instrumented single punch press (located at the research laboratories of the Department of Pharmacetuics, U.R.I.) similar to the instrumented ones. The formulas used are shown in detail in Tables I to VII.

The following tablet properties were measured: weight, thickness, diameter, hardness, disintegration time, and friability. Dissolution profiles were obtained for selected samples of the aspirin formulations. Tablet weight was determined by the use of a Mettler analytical balance[11]. A micrometer[12] was used to measure both thickness and diameter. Hardness was measured by the use of an Erweka hardness tester[13]. Twenty tablets were analyzed for weight, thickness, diameter, and hardness. Friability was determined by rotating twenty preweighed (collectively) tablets in an Erweka friabilator[16] for four minutes. The disintegration time was determined on six tablets with a USP apparatus[17] (Figure 2), with discs, in distilled water at 37°C. The dissolution profiles of the aspirin samples were determined by the use of the USP paddle apparatus[18] with 900ml of one-tenth normal hydrochloric acid at 37°C as the dissolution medium. The absorbance of the dissolution samples was determined at 265nm on a Perkin-Ellmer Hitachi spectrophotometer[19].

TABLE I

Ascorbic Acid Formula

Ingredient	Quantity per tablet (mg)
Sodium ascorbate AG[1]	199.0
Ascorbic acid 90%[2]	95.0
Microcrystalline cellulose[3]	20.0
FD&C Yellow #6[4]	1.0
Micronized silica gel[5]	4.0
Orange flavor[6]	7.4
Stearic acid[7]	40.0
Magnesium stearate[8]	2.5
Matrix	631.1
	1000.0

Sodium ascorbate, color lake, and silica gel were mixed in a Tarbula mixer[14] for three minutes. The mix was then passed through a Fitzmill[15] using #0 screen, hammer forward, at medium speed.

To the above premix, ascorbic acid, flavor, microcrystalline cellulose, and matrix were added. The ingredients were blended for five minutes, and passed through the Fitzmill with #1 plate.

The lubricants were incorporated into a small portion of the above premix, and passed through a #20 mesh screen, and added to the remainder of the premix. The blend was then mixed for ten minutes and compressed using ½ in. standard concave tooling.

TABLE II

Multivitamin Formula

Ingredient	Quantity per tablet (mg)
Ascorbic acid 90%[2]	70.0
Niacinamide[9]	24.5
Pyridoxine[10]	3.5
Riboflavin[11]	2.5
FD&C Yellow #6[4]	2.0
Flavor (orange)[6]	3.5
Magnesium stearate[8]	1.8
Matrix	242.2
	350.0

Ascorbic acid, niacinamide, pyridoxine, and riboflavin were mixed for five minutes using a Turbula mixer. The color lake, flavor, and matrix were added to the premix, and screened through #1 plate on the Fitzmill. Magnesium stearate was then incorporated into the three above mix and blended for five minutes. Standard concave 11/32 in. tooling was used.

TABLE III

Pediatric Aspirin Formula

Ingredient	Quantity per tablet (mg)
Aspirin (90%)	88.8
Starch	10.6
Talc	8.0
Stearic acid[7]	0.4
Matrix	142.2
	250.0

Aspirin was added to the matrix, and blended for five minutes. Starch and talc were added to the premix and mixed for five minutes. Stearic acid was added to the above blend and mixed for five minutes. Compression was carried out using 11/32 in. standard concave tooling.

TABLE IV

Antihistamine Formula

Ingredient	Quantity per tablet (mg)
Chlorpheniramine maleate[12]	1.0
Phenylpropranolamine Hcl[13]	6.2
Aspirin	80.0
Starch	10.0
Talc	8.0
FD&C Yellow #6[4]	0.8
Flavor (orange)[6]	2.0
Stearic acid[7]	4.0
Matrix	88.0
	200.0

Chlorpheniramine maleate, phenylpropranolamine, aspirin, color lake, and matrix were blended for five minutes and screened through the Fitzmill using a #1 plate.

Starch, talc, and flavor were added to the above premix and blended for five minutes.

Stearic acid was added, and the blend mixed for five minutes. Tablets were compressed using 11/32 in.standard concave tooling.

TABLE V

Antitussive Formula

Ingredient	Quantity per tablet (mg)
Dextromethorphan hydrobromide[14]	7.5
Pseudoephedrine hydrochloride[15]	15.0
Chlorpheniramine maleate[12]	1.0
Aspirin	325.0
FD&C Yellow #6[4]	2.0
Flavor (orange)[6]	4.0
Stearic acid[7]	10.0
Matrix	135.5
	500.0

Dextromethorphan, pseudoephedrine, chlorpheniramine, color lake, and flavor were added to the matrix and mixed for five minutes. The mixture was screened through #1 plate on the Fitzmill.

Stearic acid was added to the above blend and mixed for five minutes. The tablets were compressed at 4 to 7 kg, using 3/4 inch standard concave tooling.

TABLE VI

Antacid Formula

Ingredient	Quantity per tablet (mg)
Aluminum hydroxide/magnesium carbonate[16]	400.0
Micronized silica gel[17]	50.0
Mint flavor[18]	20.0
Magnesium stearate[8]	16.0
Matrix	1000.0
	1486.0

Aluminum hydroxide/magnesium carbonate, and silica gel were added to the matrix and mixed for five minutes. The flavor was added to the above mixture and blended for five minutes.

Magnesium stearate was added to the premix, and blended for five minutes.

Tablets were compressed at 4-7 kg, using 3/4 inch standard concave tooling.

TABLE VII

Antidiarrhea Formula

Ingredient	Quantity per tablet (mg)
Calcium carbonate[19]	350.0
Pectin[20]	32.0
Aluminum hydroxide[21]	65.0
Peppermint flavor[19]	5.0
Magnesium stearate[8]	2.5
Matrix*	1045.5
	1500.0

*Matrices:

C&H Product A[22], C&H Product B[22], C&H Product C[22], C&H Brown Matrix[22], DiPac[23], NuTab[24]

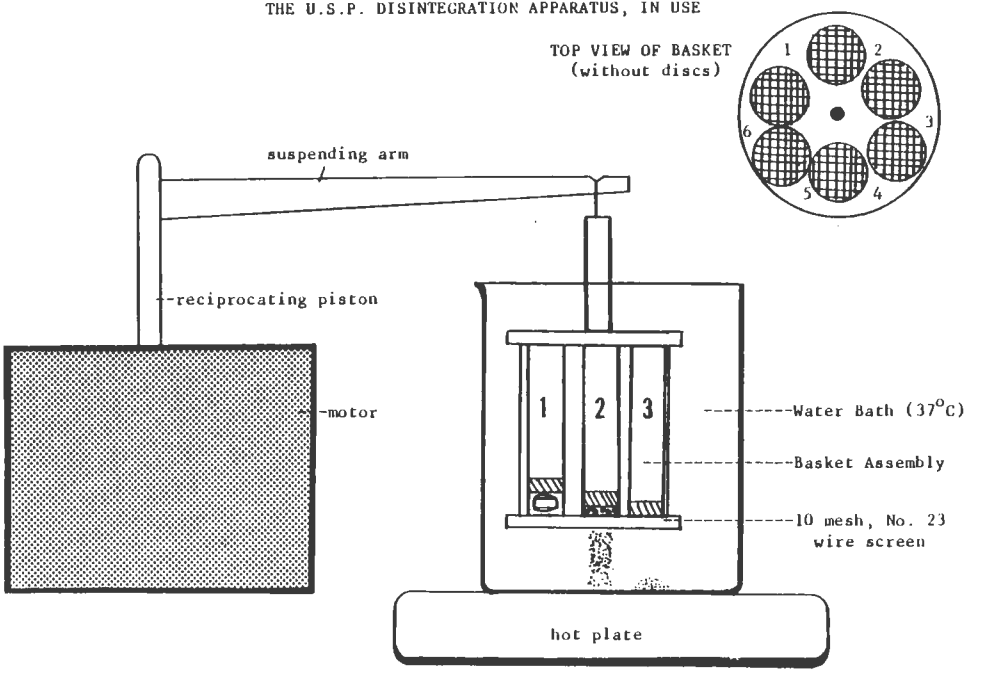
Calcium carbonate, pectin, and aluminum hydroxide were added to the matrix and mixed for five minutes. The flavor was added to the premix and blended for five minutes.

Magnesium stearate was incorporated into the above mixture and blended for five minutes.

Compression was carried out at 4 to 7 kg, using 3/4 inch standard tooling.

FIGURE 2

THE U.S.P. DISINTEGRATION APPARATUS, IN USE



(1)- no disintegration (2)- in process of disintegration (3)- disintegration completed

3. Evaluation acid neutralizing efficiency

Three matrices, C&H A, B, and Emdex, were formulated into antacid tablets. Three tablets from each batch were tested (individually) for "acid neutralizing efficiency". The apparatus used consisted of a pH meter which was electronically connected to a strip chart recorder[5]. The tablet sample to be tested was place in 100ml of one-tenth normal hydrochloric acid (preheated to 37°C) contained in 250ml beaker. The beaker was placed on a hot plate/magnetic stirrer[20]. The heating level was set to mentain the temperature of the hydrochloric acid solution at 37 ± 1°C. A two and half centimeter, Teflon coated, stirring bar was used to agitate the tablet at 300 rpm. The pH electrodes (prestandardized to pH 1) were then lowered into the solution to an optimum level not to interfere with the agitation, and the chart recorder simultaneously turned to the recording mode. The chart speed was kept constant at 1cm/min.. Thus, the change in the pH of the acid medium was recorded as a function of time (pH profiles). Tablet samples were analyzed two days after manufacture and at the end of a short term aging study.

In order to determine the effect of aging on the direct compression antacid tablets, samples of the tablets, in amber colored bottles, were stored under three conditions: room temperature (approximately 25°C), 30°C with 80% relative humidity-cyclic, and 30°C with 80% relative humidity-constant. The samples exposed to the cyclic conditions were kept in a desiccator at 80% relative humidity in a 30°C oven for twelve hours. The bottles containing these samples were removed from the desiccator at the end of the twelve hours, and kept in room conditions for twelve hours. This cycle was repeated daily for three months. Those samples exposed to 30°C/80% relative humidity-constant, were kept

in the desiccator (within the 30°C oven) throughout the test period. At the end of the test period, the tablets were analyzed for both physical properties and acid neutralizing efficiency.

4. The effect of aging on the disintegration and dissolution of selected coated tablets

The major limitation of sucrose-based direct compression matrices is their high hydroscopicity. The degree of moisture up-take can be significantly reduced by coating the tablets. However, little has been done to determine the adaptability of the various types of coating to high temperature and humidity conditions, such as those that prevail in tropical regions of the world. Therefore, a study was carried out to investigate the effect of short term moderate storage stress on the disintegration and dissolution of selected coated tablets. The tablets used represent each of the main coating processes currently used in industry. Commercially available samples of sugar coated chlorpromazine[25] (50mg), film coated chlorpromazine (50mg)[26], and enteric coated aspirin 325mg[27] were used. Prednisone 10mg (plain)[28], a dissolution apparatus calibrator, was also evaluated.

Samples of tablets, twelve to a bottle, were stored in amber safety-locked bottles and exposed to one of the following:

A - room temperature, approximately 20°C

B - cyclic (12 hours 30°C, 12 hours room temperature)

C - 30°C isothermal

D - cyclic (12 hours 30°C with 90% relative humidity, 12 hours room temperature)

E - 30°C isothermal with 90% relative humidity.

The samples were kept in these conditions for up to four weeks.

The temperatures were controlled to $\pm$ 1°C and relative humidity was controlled to $\pm$ 5%.

At the end of the four week storage period, disintegration times were determined for six tablets using the USP method, with discs. Dissolution profiles (plots of percent drug dissolves as a function of time) were obtained by the use of a six unit USP paddle dissolution apparatus in conjunction with an automatic ultra-violet spectrophotometer[21] (located at the Food and Drug Administration's Biopharmaceutics Laboratories, Washington, DC). The λ max values for the three drugs: chlorpromazine, aspirin, and prednisone were found to be 254, 265, and 242 nM respectively. The speed of agitation was kept constant, 50 rpm. A cell path length of 1 cm was used for chlorpromazine and prednisone, and 0.1 cm for aspirin. Absorbance values were recorded at a number of time intervals for periods of up to sixty minutes. In order to obtain the so called t_∞ reading, which represents the total amount of drug in each individual tablet, the speed of the paddles was increased from 50 to 200 rpm and additional samples taken until the rate of change in optical absorbance with time became zero. Thus, the dissolution data obtained in this study can be expressed in terms of either percent of label claim or percent of drug found in each tablet, as indicated by t_∞ readings. The dissolution media used were: one-tenth normal hydrochloric acid (900ml) for both sugar coated chlorpromazine and film coated chlorpromazine, and dearated water (500ml) for prednisone. Two different media were used for enteric coated aspirin, 900ml of 0.1N HCl during the first hour of each dissolution run, and then 900ml of pH 7.4 phosphate buffer. The dissolution data was plotted in the form of percent drug dissolved as a function of time; mean and standard deviations were determined at each sampling time.

RESULTS AND DISCUSSION

A. Characterization of direct compression sugars

1. Intrinsic properties of bulk powders

Moisture content, measured as loss on drying, of a direct compression vehicle is an extremely important property. Formulation variables such a lubrication, and compressibility may indeed depend on moisture content. It is particularly important that the moisture content of a sugar based matrix be carefully regulated as these systems may pick up additional moisture from the environment during storage. Table VIII lists the moisture content of the matrices investigated. All the matrices had moisture levels that were within what is generally regarded as the optimum range, 0.75 - 2% (2).

Density, both bulk and tap, is another major intrinsic property of a direct compression matrix. This property contributes substantially to the overall flow characteristics of given system. Table IX lists both bulk and tap densities for the material studies. Apparent differences in densities were observed between C & H AI and C & H AII although these were identical products (in the process of manufacture). The products were manufactured by the same method with all processes being similar, including final sieving. It is thought that since this particular matrix is processed in such a manner as to attain a soft texture, more like a popcorn, fracture of the particles may occur during packaging. Thus, lot to lot, or within lot variability may occur. However, C & H B, a more compact material did not show any significant lot to lot variation in particle density.

Among the intrinsic properties of an uncompressed powder system, particle size distribution is perhaps the most important. For many

TABLE VIII

Moisture Content of Matrices

Matrix	Moisture content (%)*
C & H AI	0.3
C & H AII	0.3
C & H B	0.5
C & H Brown	1.0
DiPac	0.3
NuTab	0.4

*Loss on drying (n = 3)

TABLE IX

Powder Density

Matrix	Density (gm/ml) Bulk	Tap
C & H AI	0.561	0.689
C & H AII	0.476	0.613
C & H B	0.674	0.784
C & H Brown	0.553	0.654
DiPac	0.665	0.806
NuTab	0.728	0.828

*Material was tapped for 1000 cycles on a motorized tapper.

systems, such as was observed here, a change in particle size spectra will result in changes in density, flow characteristics, and compressibility. Figure 3 is a plot of the particle size distribution for the matrices studied. The percentage (weight) of powder accumulating at the specified sieve aperture was plotted on a probability graph. This approach yields a linear plot compared to the sigmoidal curves that would result from the plot of cummulative amounts versus aperture size on linear-linear scale. Figure 4 shows the particle size distribution for the two batches of C & H A (I and II). C & H AI showed a mean particle size (corresponding to 50% point on the ordinate) of 250μm, whereas C & H AII had a mean particle size of 150μm. This difference in particle size distribution may account for differences observed in both flow and compressibility of the two matrices.

As has been alluded to, particle size distribution of a direct compression system is of profound importance. This is exemplified when the flow data obtained in this study are examined (Table X). C & H AI with a mean particle size of 250μm had a flow rate of 170 gm/sec, whereas C & H AII, with a mean particle size of 150μm, had a flow rate of only 75.7 gm/sec.

In addition to intrinsic flow properties (unlubricated matrices alone), formulation mixtures as outlined in Tables I through VII were also studied in a similar manner. A recording powder flowmeter was used in both cases. This enabled the determination of mass flow, gm/sec (flow rate) i.e. how fast the material could flow, and linearity of the flow (the evenness of the flow). The latter, although equally important, is to a degree dependent on the configuration of the hopper used. It is generally regarded that for an adequate flow, a matrix should exhibit a mass flow value of 75 gm/sec and a linearity value not less than 15. In tables XI and XII

TABLE X

Intrinsic Flow Properties

Matrix	Mean[1] Mass flow (gm/sec)	Mean[2] Linearity
C & H AI	180.8	19.5
C & H AII	75.7	17.4
C & H B	231.4	19.6
C & H Brown	48.5	18.6
DiPac	161.9	18.7

[1] $n = 3$

[2] Linearity = $(r^2 - 0.8) \times 100$

FIGURE 3

PROBABILITY PLOT FOR MATRIX PARTICLE SIZE

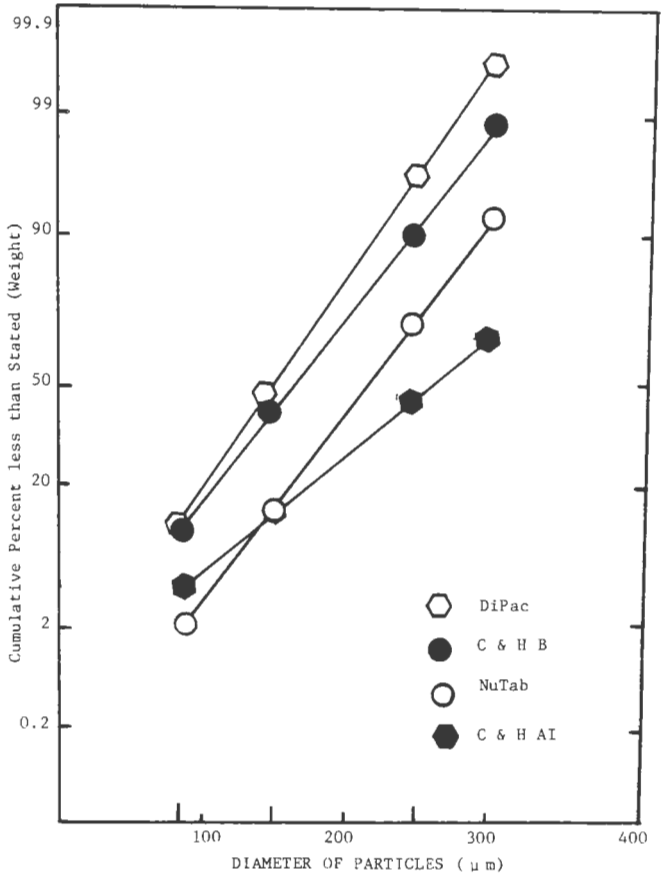
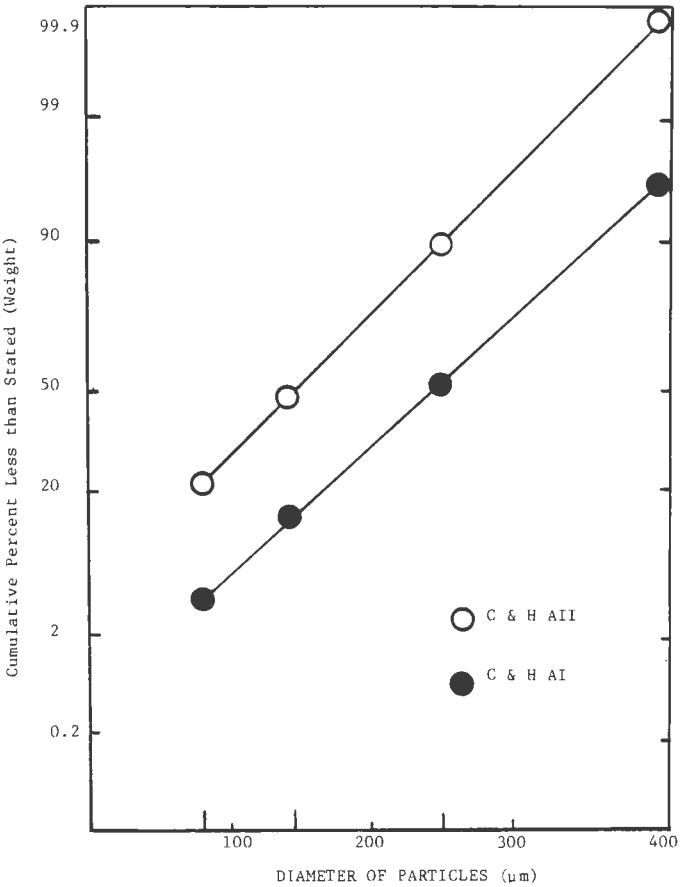


FIGURE 4

PROBABILITY PLOT FOR PARTICLE SIZE OF TWO SAMPLES OF C&H A



C & H B shows the best overall flow characteristics.

In direct compression, the capacity, i.e. the amount of an active ingredient that can be incorporated into a matrix, without causing significant formulation problems, is of considerable importance. One of the properties of a formulation or powder system that may change with increase in percent active, is the flow behavior. Figure 5 shows the effect of increasing levels of ascorbic acid on the flow behavior of the matrices. When ascorbic acid was incorporated at twenty five percent level, the flow rate of C & H B remained unchanged, whereas that of C & H AI and DiPac decreased significantly. Further increase of the levels of ascorbic acid to thirty five percent produced decreases in the flow rate for all the three products studied. (C & H AI, C & H B, and DiPac). However, an increase over thirty-five percent did not produce further reduction in flow rate. It may be noteworthy that these levels were chosen arbitarily around thirty percent (regarded as the average capacity of most direct compression vehicles). Nevertheless, this level may be different with different active ingredients.

2. Morphology of bulk powders

Samples of the matrices were photographed using a scanning electron microscope. Figures 6 to 11 show the micrographs of the matrices at approximately the same magnification. It can be discerned that the particles of NuTab and Emdex are almost spherical, with relatively smooth edges. The particles of C & H AI (A) appear to be the smallest among the group. Although there appears to be considerable similarity between the particles of DiPac and C & H B, the surface of C & H B particles show discrete crystals (cubes). It may well be the relatively clean surface of this particles that affords the product its excellent com-

TABLE XI

Flow Properties - Mass Flow (gm/sec)

Formulation	C & H AII	Matrix C & H B	DiPac
Calcium carbonate/ aluminum hydroxide	56.2	126.7	85.4
Dextromethorphan HBr	85.6	243.9	126.2
Chlorpheniramine maleate/ phenylpropranolamine Hcl	65.5	131.2	89.8
Aspirin	49.2	211.0	133.2

TABLE XII

Flow Properties - Linearity*

Formulation	Matrix C & H AII	C & H B	DiPac
Calcium carbonate/ Aluminum hydroxide	16.6	16.2	16.9
Dextromethorphan HBr	18.3	19.1	18.3
Chlorpheniramine maleate/ phenylpropranolamine Hcl	14.1	17.1	15.1
Aspirin	11.2	18.6	15.6

*Linearity = $(r^2 - 0.8) \times 100$, n = 3

FIGURE 5

EFFECT OF INCREASE IN PERCENT ACTIVE (ASCORBIC ACID) ON MASS FLOW

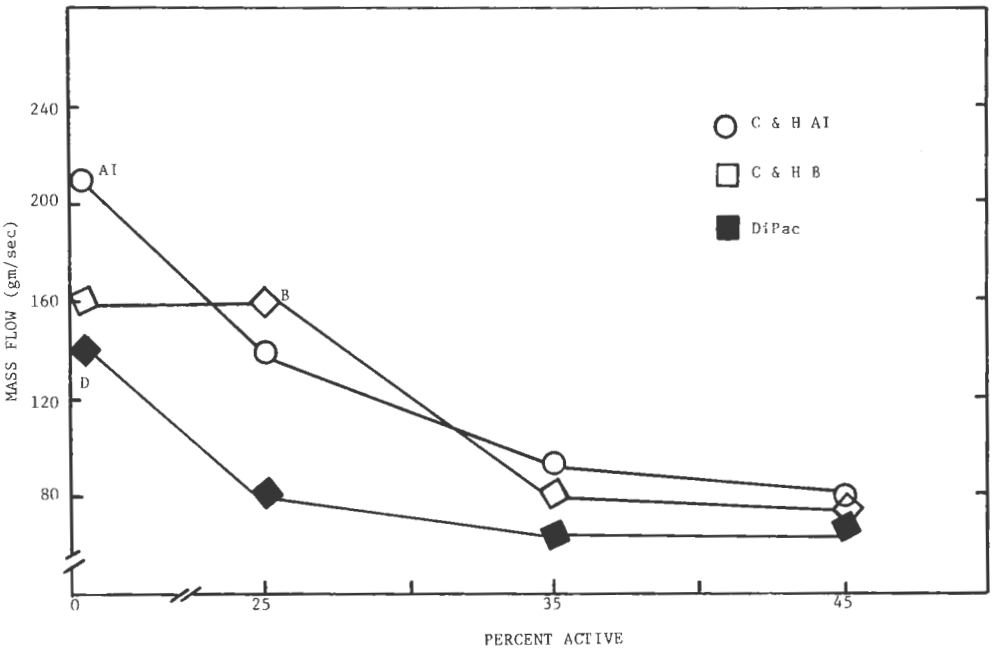


FIGURE 6

SCANNING ELECTRON MICROGRAPH - C&H AI

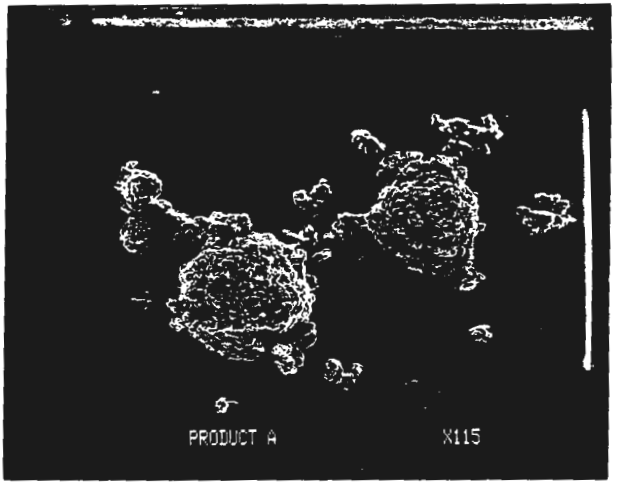


FIGURE 7

SCANNING ELECTRON MICROGRAPH - C&H B

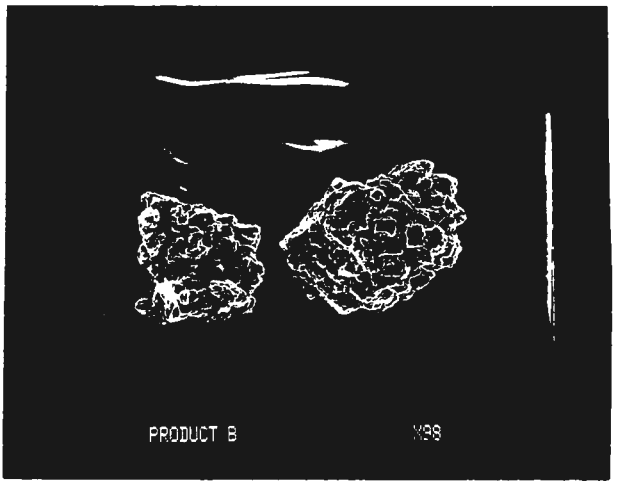


FIGURE 8

SCANNING ELECTRON MICROGRAPH - C&H C

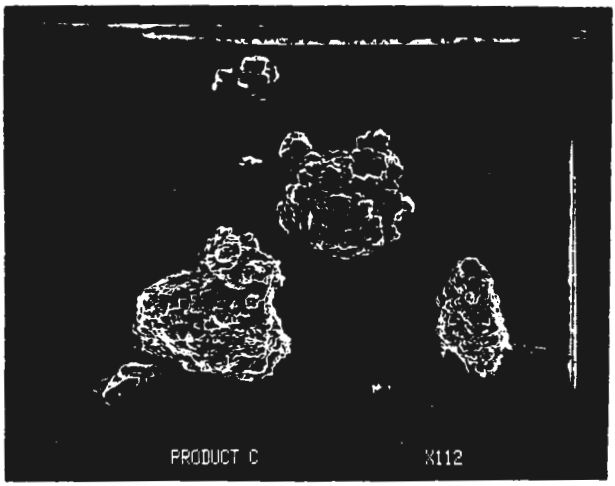


FIGURE 9

SCANNING ELECTRON MICROGRAPH - DIPAC

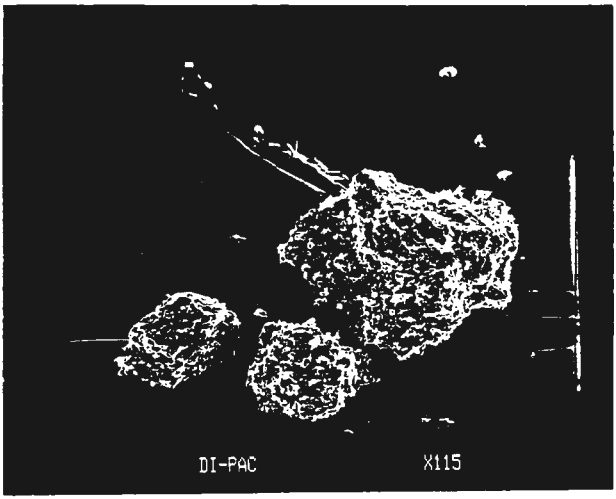


FIGURE 10

SCANNING ELECTRON MICROGRAPH - NUTAB

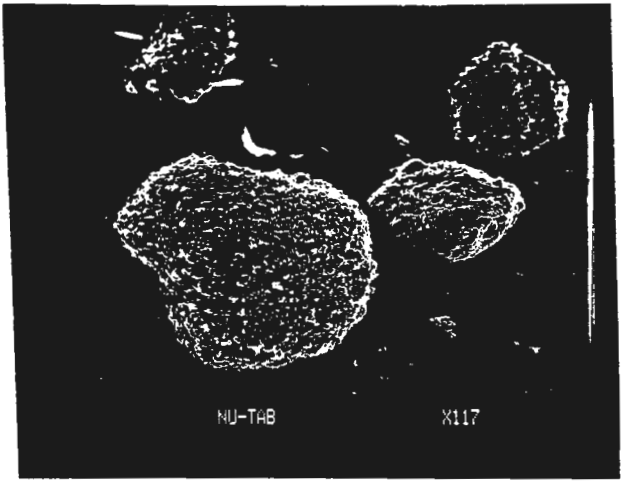
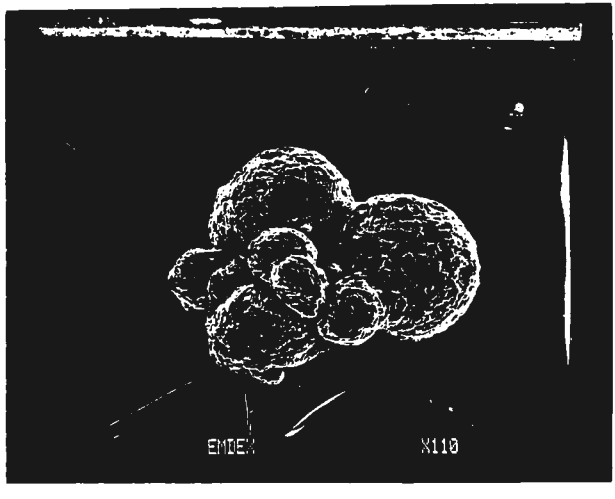


FIGURE 11

SCANNING ELECTRON MICROGRAPH - EMDEX



pressibility, while maintaining adequate flow.

3. Compression parameters and tablet properties

One of the objectives of this study was to use a computerized, instrumented tablet press to screen a series of new direct compression matrices. In order to achieve this, the following compression curve parameters were generated: height (peak), inflection point ordinate, maximum slope, area under the curve, center, and width (at mid height). Three of the investigational matrices, C & H AI, B, and C, were lubricated with one-half a percent of magnesium stearate and compressed to obtain the above mentioned parameters. Figure 1 shows a typical compression curve. The parameters used to define the curve have been illustrated. The tablets were compressed at four compressional force levels. Table XIII shows the compression curve parameters measured. Maximum slope, inflection point ordinate, and area under the curve were found to vary linearly with maximum compressional force. Area:height (A:H) may be related to the energy expended during the compaction process. This parameter may also be related to the inherent compressibility of a system as shown by Chilamkurti and coworders (123). Since area under the compression curve is related to the work done, then A:H is a measure of the time required to transmit a given amount of energy to a system. Therefore, it is likely that the greater the A:H value, the less the inherent compressibility. The three products investigated for compression curve parameters (C & H AI, B, and C) showed significant differences in the A:H values. i.e. indicating differences in compressibility. This was paralled by differences in the ease of tablet press operation at the same setting for the three matrices.

Systems with high Smax:H values have the capacity to accept energy, i.e. have work done on them, at a greater rate than those with low

TABLE XIII

Compression curve parameters for lubricated matrices

Matrix	A:H Value, Sec x 10^3	Intercept, N. Sec	R^2(Number of Points)
A	54.93	-0.086	0.99 (4)
B	59.04	-0.2065	0.99 (4)
C	61.34	-0.2466	0.99 (4)

	1PO:H Value (x10^2)	Intercept, N	R^2(Number of Points)
A	57.34	0.2479	0.99 (4)
B	54.53	0.5057	0.99 (4)
C	55.03	0.4724	0.99 (4)

	S_{Max}:H Value, Sec^{-1}	Intercept, N. Sec^{-1}	R^2(Number of Points)
A	23.79	16.77	0.99 (4)
B	23.46	57.13	0.99 (4)
C	22.22	75.61	0.99 (4)

A:H - Area:Height

1PO:H - inflection point ordinate:height

S_{Max}:H - Maximum slope:height

R^2 - correlation coefficient

Smax: H values. The three varieties of C & H products did not show significant difference in Smax:H values (Table XIII). Chilamkurti (123) has also shown that there was no significant difference in this parameter for two types of dicalcium phosphate dihydrate. It is conceivable that this parameter is inherent of the chemical properties of a system.

Inflection point ordinate, slope (maximum), and area under the curve varied linearly with applied force, Figures 12, 13, and 14 respectively. Disintegration time appeared to be independent of tablet hardness (Figure 15), probably due to the fact that these water soluble matrices form tablets which undergo erosion as opposed to disintegration per se. This phenomenon of erosion has been compared to the peeling of an onion, one layer at a time.

Physical properties of the tablets made from the lubricated matrices (C & H AI, B, and C) are shown in Tables XIV-XVI. As expected from satisfactory flow data, weight uniformity for all the three matrices was excellent. Tablet thickness decreased with increase in applied force. Both C & H AI and C & H B showed increases in friability when tableted at high compressional forced (Table XV). This increase in friability was observed although hardness appeared to have increased with higher compressional forces.

Figures 16 and 17 show the effect of compressional force on the hardness of tablets made from lubricated matrices (C & H AI, B, and C). The hardness values used in Figure 16 were obtained immediately after compression, while those hardness values used in Figure 17 were obtained forty five days after manufacture. There appears to be an aging process in which a reduction in tablet harndess occurs.

All the matrices investigated except the Brown sugar, were incorpo-

FIGURE 12

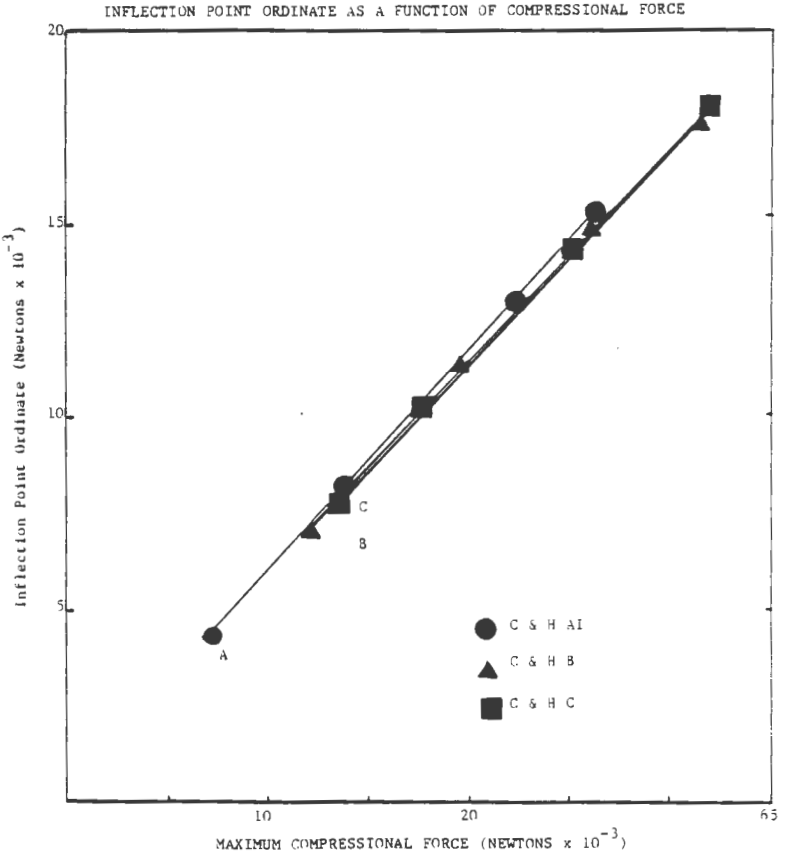

INFLECTION POINT ORDINATE AS A FUNCTION OF COMPRESSIONAL FORCE
Inflection Point Ordinate (Newtons x 10^{-3})
20
15
10
5
A
B
C
C & H A1
C & H B
C & H C
10
20
65
MAXIMUM COMPRESSIONAL FORCE (NEWTONS x 10^{-3})

FIGURE 13

MAXIMUM SLOPE AS A FUNCTION OF COMPRESSIONAL FORCE

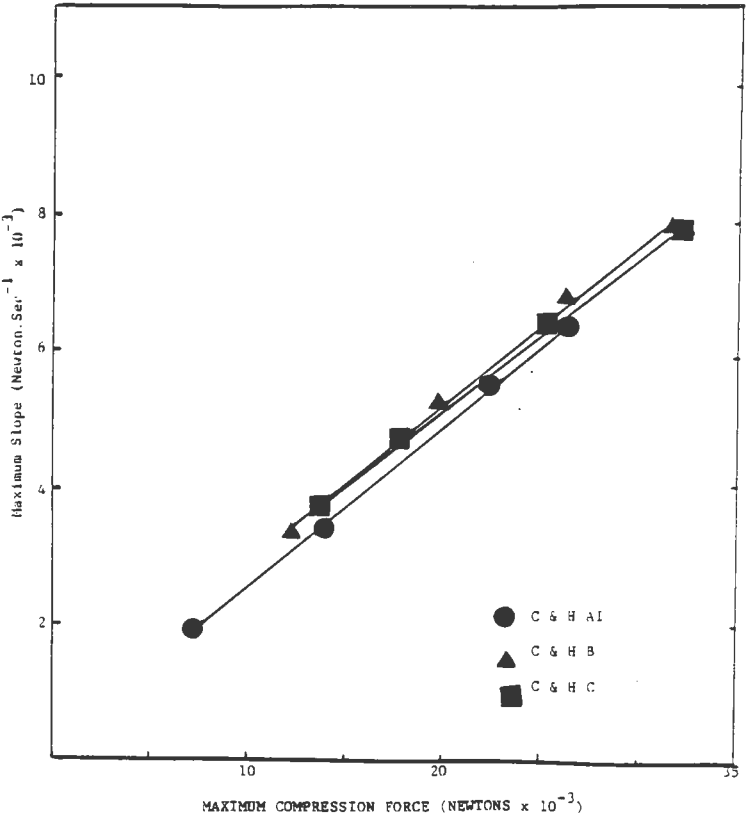


FIGURE 14

AREA AS A FUNCTION OF COMPRESSIONAL FORCE

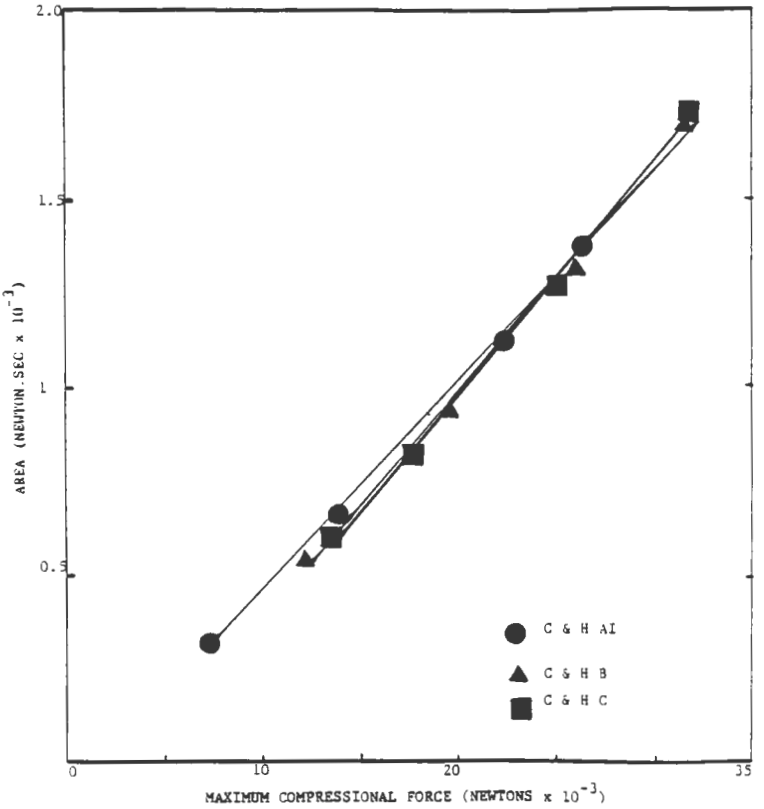


FIGURE 15

DISINTEGRATION AS A FUNCTION OF HARDNESS

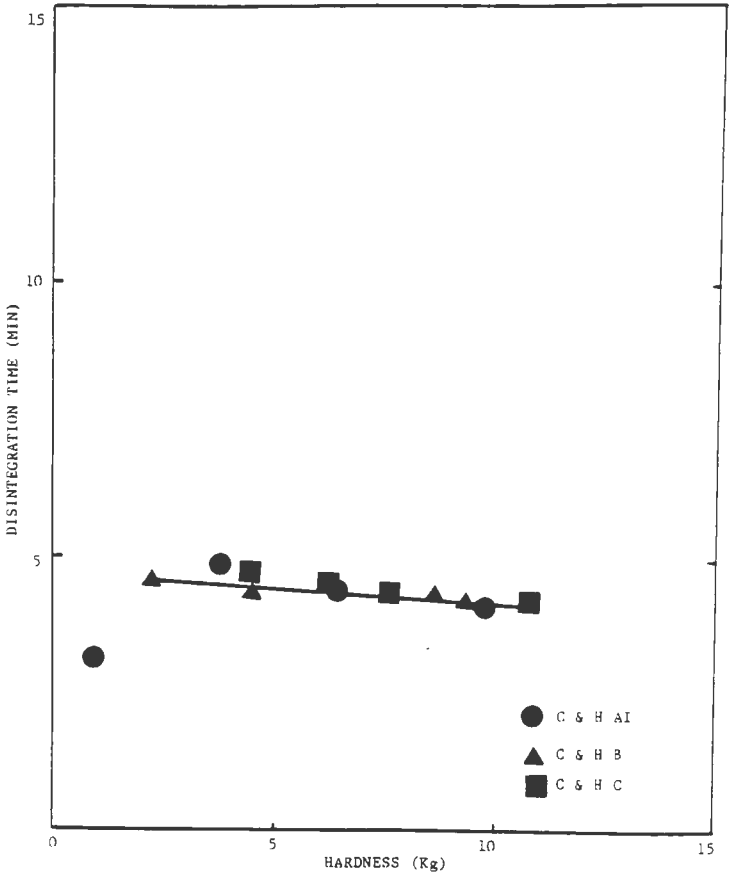


TABLE XIV

Tablet Properties for Lubricated Matrices

Matrix Replicate	Compressional Force (Newtons x 10^{-3})	Weight (mg) Means	Weight (mg) R.S.D.	Thickness (mm) Mean	Thickness (mm) R.S.D.
C & H AI					
1	7.2	292.4	0.71	3.27	0.34
2	13.8	329.5	0.78	3.34	0.48
3	22.3	300.7	0.54	2.87	0.27
4	26.3	294.1	0.30	2.77	0.45
C & H B					
1	12.2	303.1	0.45	3.07	0.29
2	19.6	301.7	0.59	2.91	0.48
3	26.1	298.1	0.62	2.80	0.47
4	31.5	298.7	0.87	2.76	0.53
C & H C					
1	13.5	302.3	0.44	3.04	0.27
2	17.6	305.2	0.37	2.98	0.55
3	25.1	299.3	0.63	2.83	0.36
4	31.9	298.8	1.27	2.76	0.88

TABLE XV

Tablet Properties for Lubricated Matrices

Matrix Replicate	Compressional Force (Newtons x 10^{-3})	Hardness (Kg) Mean	R.S.D.	Friability Percent
C & H AI				
1	7.2	0.90	14.34	1.47
2	13.8	3.75	6.29	1.58
3	22.3	6.43	13.36	2.16
4	26.3	9.78	18.84	2.67
C & H B				
1	12.2	2.26	9.49	1.93
2	19.6	4.56	7.75	1.69
3	26.1	8.67	7.24	2.64
4	31.5	9.36	9.95	2.46
C & H C				
1	13.5	4.46	4.89	2.97
2	17.6	6.28	9.39	2.98
3	25.1	7.62	9.88	2.88
4	31.9	10.82	6.34	2.60

TABLE XVI

Disintegration Time for Placebo Tablets

Matrix Replicate	Compressional Force (Newtons x 10^{-3})	Disintegration time (Min) Mean	Range
C & H AI			
1	7.2	3.14	2.83 - 3.50
2	13.8	4.86	4.50 - 5.50
3	22.3	4.36	3.75 - 4.58
4	26.3	4.10	3.67 - 4.75
C & H B			
1	12.2	4.53	4.17 - 5.17
2	19.6	4.31	4.16 - 4.50
3	26.1	4.25	3.75 - 4.58
4	31.5	4.14	3.67 - 5.00
C & H C			
1	13.5	4.68	4.00 - 5.67
2	17.6	4.50	4.16 - 4.83
3	25.1	4.30	4.08 - 4.67
4	31.9	4.19	3.67 - 4.75

FIGURE 16

HARDNESS AS A FUNCTION OF COMPRESSIONAL FORCE

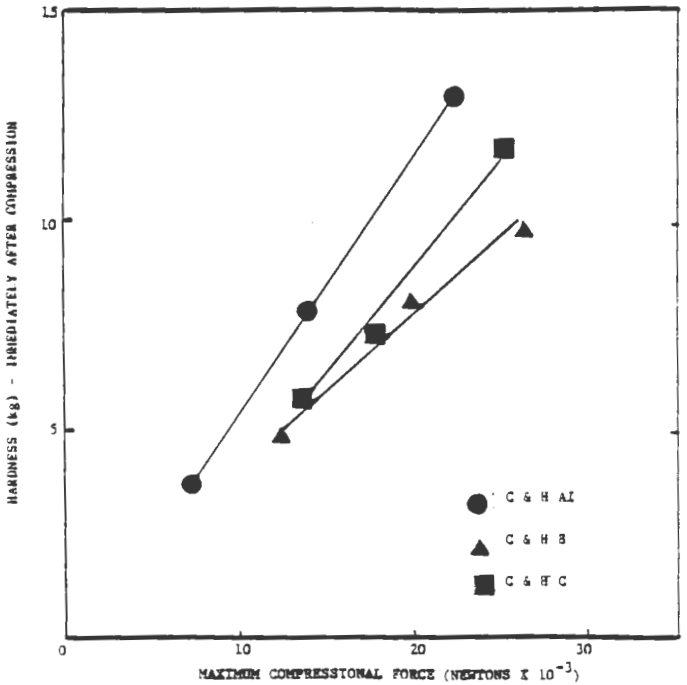
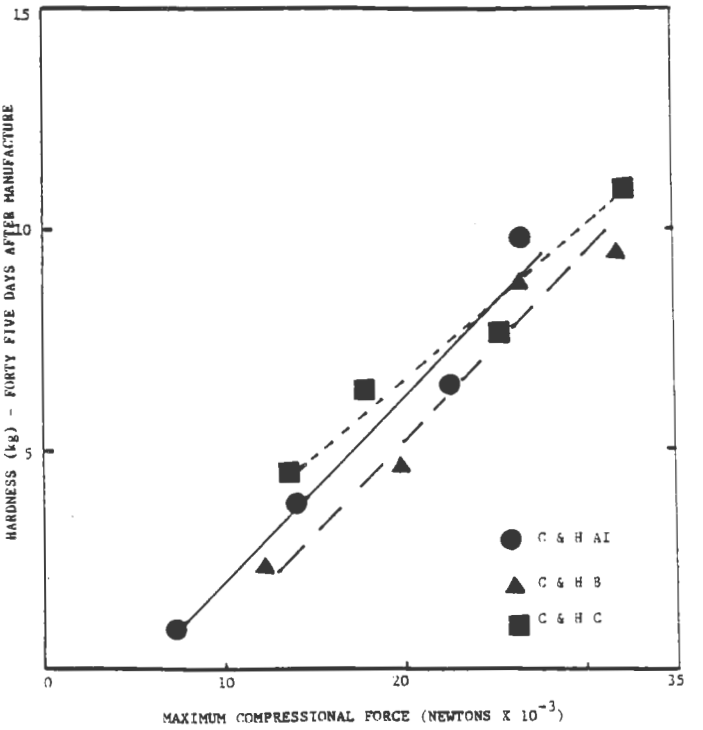


FIGURE 17

HARDNESS AS A FUNCTION OF COMPRESSIONAL FORCE



rated into a pediatric aspirin formulation. The aspirin used was a 10% starch granulated type for direct compression. This type of aspirin was chosen over the crystalline material to enable the study of the formulation variables, such as compressional forces, on the release of an active ingredient from a sugar matrix (water soluble) where tablet disintegration occurs through a combination of matrix erosion, and actual particle disintegration (starch-aspirin granules). Table XVII and XVIII show the physical properties of the aspirin tablets made at different compressional forces. Figure 18 represents the effect of compressional forces on tablet hardness. It was observed that C & H AI produced the hardest tablets at all compressional forces.

Figure 19 illustrates the effect of compressional force on tablet thickness. As expected, there is an initial decrease in thickness with increase in compressional force; the upper punch traveling much deeper into the die cavity with the adjustment on the pressure setting to compress the tablet harder. At compressional forces greater than ten thousand Newtons, no change in tablets thickness is produced with increase in compressional force. At such compaction levels is conceivable that a majority of the void spaces have been occupied by particles. Further compaction produces particle interaction with no appreciable change in the overall volume of the tablet.

Figure 20 is a plot of the effect of compressional force on the friability of the aspirin tablets. C & H B and DiPac, two of the matrices that showed some similarity in morphology, particle size distribtuion and density, showed identical, almost superimpossible, profiles. C & H AI and AII had similar profiles. However, the profile observed for those tablets made from NuTab was very different. The tablets showed higher

TABLE XVII

Physical Properties for Aspirin Tablets

Matrix Replicate	Compressional Force (Newtons x 10^{-3})	Hardness (Kg) Mean	R.S.D.	Friability Percent
C & H AI				
1	2.7	0.47	29.78	1.48
2	4.1	0.78	38.46	1.00
3	8.0	2.32	16.71	0.40
4	15.5	4.92	9.75	0.50
5	17.1	4.95	9.29	0.40
C & H AII				
1	2.0	0.70	21.42	0.80
2	3.0	3.67	17.71	0.40
3	8.0	6.27	7.97	0.30
4	10.2	7.75	10.96	0.30
5	16.4	7.35	12.92	0.30
C & H B				
1	3.0	0.75	40.00	4.0
2	3.8	2.45	20.40	0.40
3	8.9	3.70	7.56	0.40
4	10.3	5.08	8.66	0.30
5	18.4	6.20	14.51	0.40

TABLE XVII (Continued)

Physical Properties for Aspirin Tablets

Matrix Replicate	Compressional Force (Newtons x 10^{-3})	Hardness (Kg) Mean	R.S.D.	Friability Percent
DiPac				
1	3.0	0.32	37.50	*
2	4.7	0.72	37.50	4.00
3	9.0	1.80	20.00	0.80
4	17.1	4.32	9.02	0.10
5	19.8	5.07	10.84	0.30
NuTab				
1	3.0	0.25	-	*
2	5.6	0.38	34.20	*
3	7.3	0.88	27.27	0.80
4	16.3	2.07	15.45	0.90
5	21.3	3.35	8.65	1.70

*

All Tablets broke into small pieces

TABLE XVIII

Physical Properties for Aspirin Tablets

Matrix Replicate	Compressional Force (Newtons x 10^{-3})	Weight (mg) Mean	Weight (mg) R.S.D.	Thickness (mm) Mean	Thickness (mm) R.S.D.
C & H AI					
1	2.7	254.1	0.94	4.41	0.36
2	4.1	247.6	0.85	4.24	0.57
3	8.0	274.4	0.73	3.98	0.55
4	15.5	248.5	0.66	3.86	0.57
5	17.1	249.8	0.72	3.86	0.50
C & H AII					
1	2.0	247.5	0.83	4.26	0.43
2	3.0	249.9	1.56	4.01	0.46
3	8.0	249.0	1.13	3.88	0.76
4	10.2	248.7	1.00	3.83	0.70
5	16.4	246.3	1.04	3.75	1.12
C & H B					
1	3.0	250.5	0.55	4.14	0.78
2	3.8	252.1	1.31	4.01	0.59
3	8.9	251.3	0.67	3.93	0.64
4	10.3	250.6	0.73	3.83	1.05
5	18.4	253.6	1.41	3.83	1.10

TABLE XVIII (Continued)

Physical Properties for Aspirin Tablets

Matrix Replicate	Compressional Force (Newtons x 10^{-3})	Weight (mg) Mean	Weight (mg) R.S.D.	Thickness (mm) Mean	Thickness (mm) R.S.D.
DiPac					
1	3.0	251.3	0.99	4.34	0.46
2	4.7	250.9	0.84	4.19	0.69
3	9.0	253.5	1.00	4.06	0.78
4	17.1	253.2	1.06	3.93	0.90
5	19.8	251.9	0.88	3.88	0.75
NuTab					
1	3.0	255.2	1.66	4.21	0.64
2	5.6	259.2	1.18	4.16	0.62
3	7.3	256.5	1.40	4.06	0.62
4	16.3	256.1	0.98	3.96	0.89
5	21.3	258.7	1.38	3.93	1.05

FIGURE 18

HARDNESS AS A FUNCTION OF COMPRESSIONAL FORCE
(ASPIRIN FORMULATION)

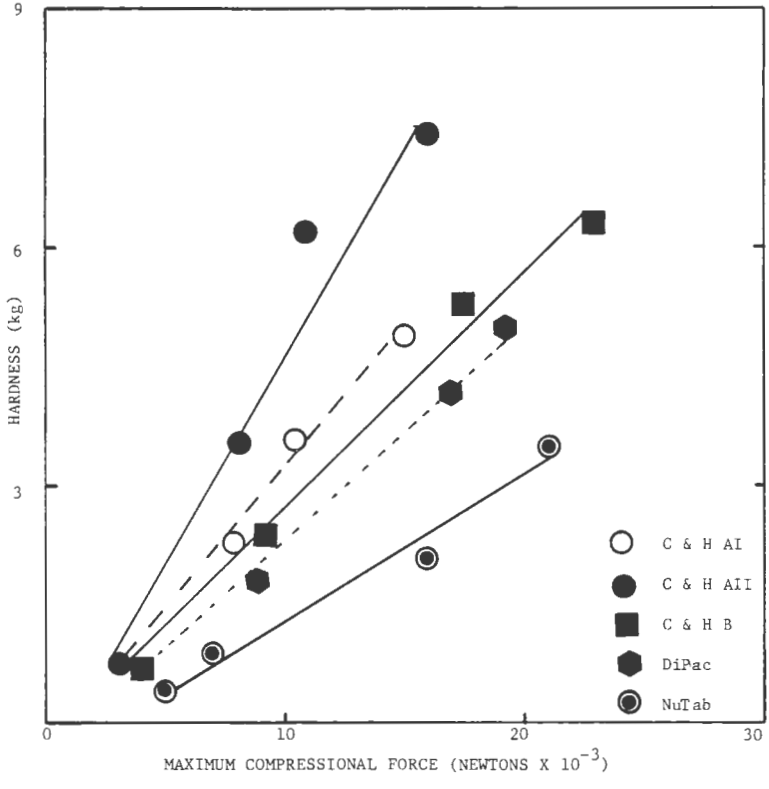


FIGURE 19

THICKNESS AS A FUNCTION OF COMPRESSIONAL FORCE
(ASPIRIN FORMULATION)

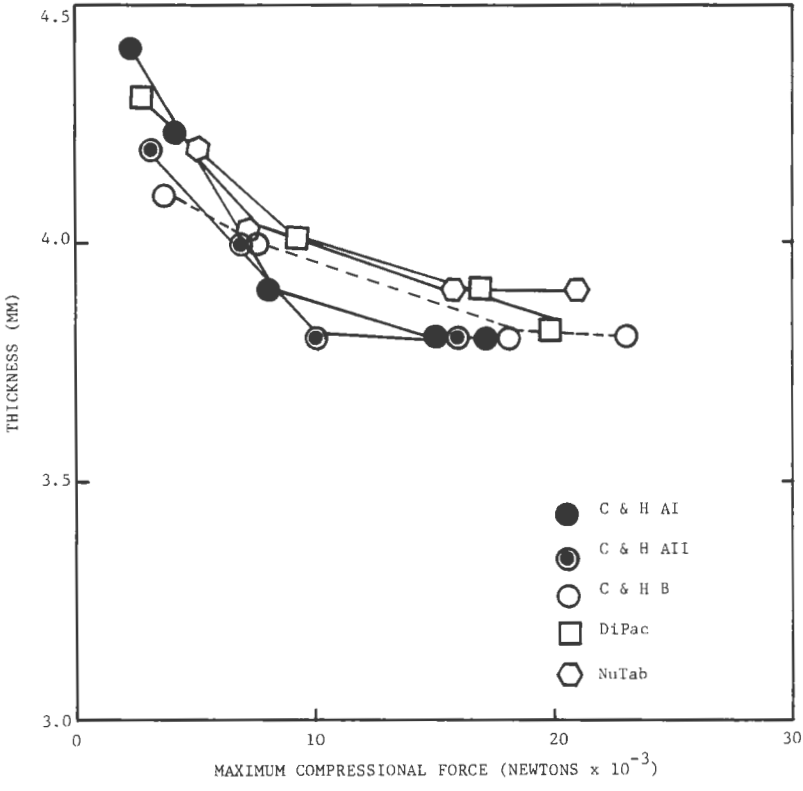
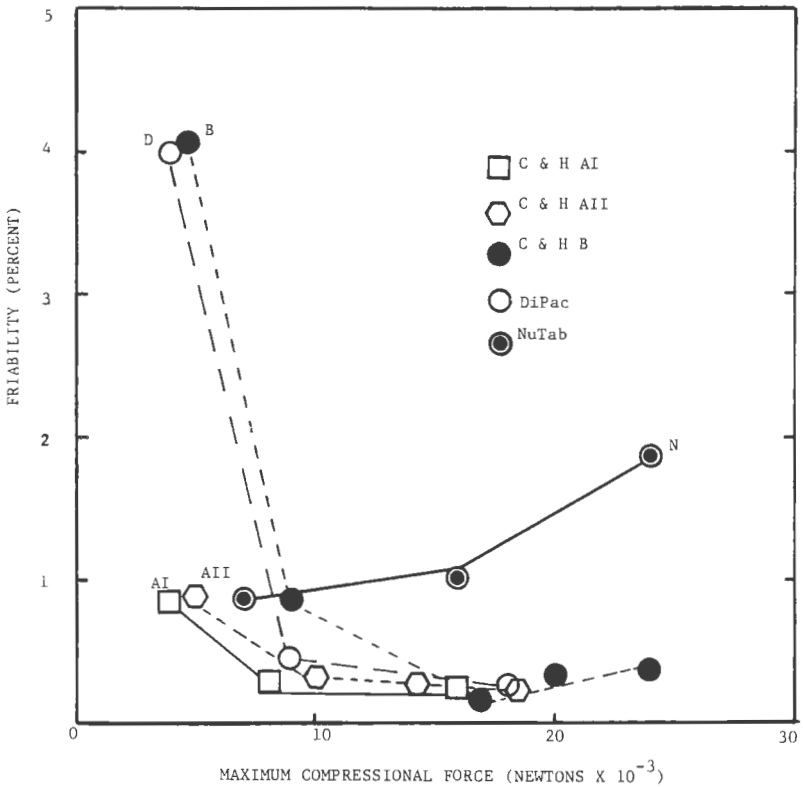


FIGURE 20

FRIABILITY AS A FUNCTION OF COMPRESSION FORCE
(ASPIRIN FORMULATION)



friability when produced at higher compressional forces.

Figure 21 illustrates the relationship between tablet hardness and friability for the aspirin formulation. Similar trends, as those noted in friability versus compressional forces were observed. C & H B and DiPac showed identical profiles. Likewise, C & H AI and C & H AII had identical profiles. However, NuTab displayed an increase in friability with increases in hardness.

The effect of compressional force on the disintegration of the aspirin tablets is presented in Figure 22. Tablets made with C & H AII showed the highest overall disintegration time, whereas tablets made from C & H AI showed the lowest disintegration times (disintegrated most rapidly). Those tablets made from the other three matrices (C & H B, DiPac, and NuTab) had similar disintegration profiles.

Figure 23 shows the relationship between hardness and disintegration for the aspirin formulation. Although it can not be pointed out as to which of the two parameters is the independent variable, and which is the dependent variable, such a plot allows the visualization of the relationship between the two tablet properties. A general trend of an increase in disintegration time with increase in hardness was observed. C & H AII showed a sharp increase in disintegration time when tablet hardness exceeded five kilograms. Although nothing conclusive can be drawn from this particular observation, since C & H AII was the only matrix that was compressed over five kilogram tablet hardness, it quite conceivable that at hardness levels above five kilograms, tablet penetration by water is much slower compared to penetration in softer tablets.

Figures 24 through 28 show dissolution profiles for aspirin tablets made at four different compressional force for each matrix, C & H AI,

FIGURE 21

FRIABILITY AS A FUNCTION OF HARDNESS
(ASPIRIN FORMULATION)

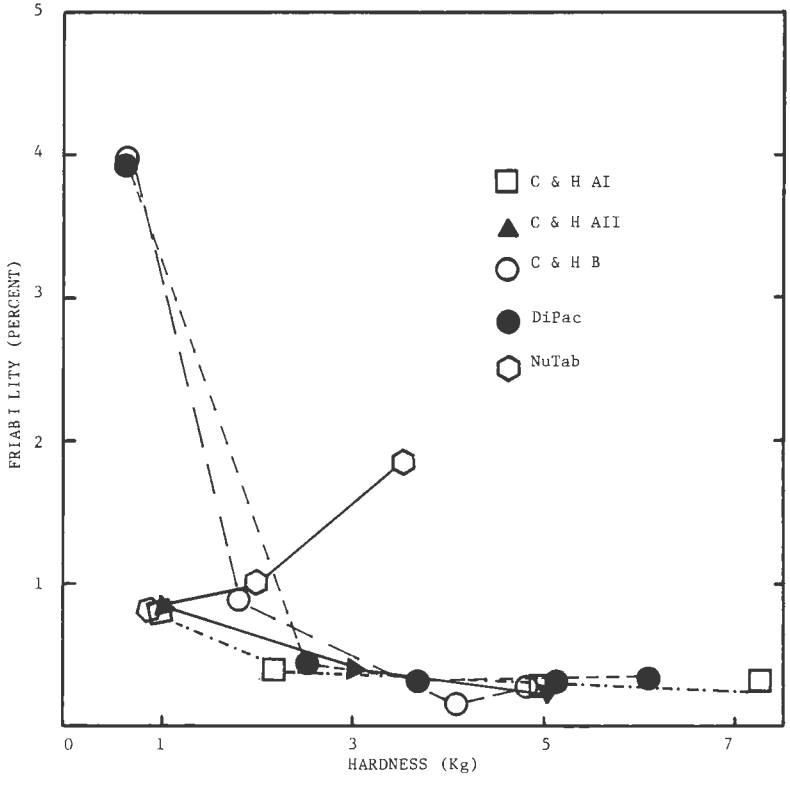


FIGURE 22

DISINTEGRATION AS A FUNCTION OF COMPRESSIONAL FORCES
(ASPIRIN FORMULATION)

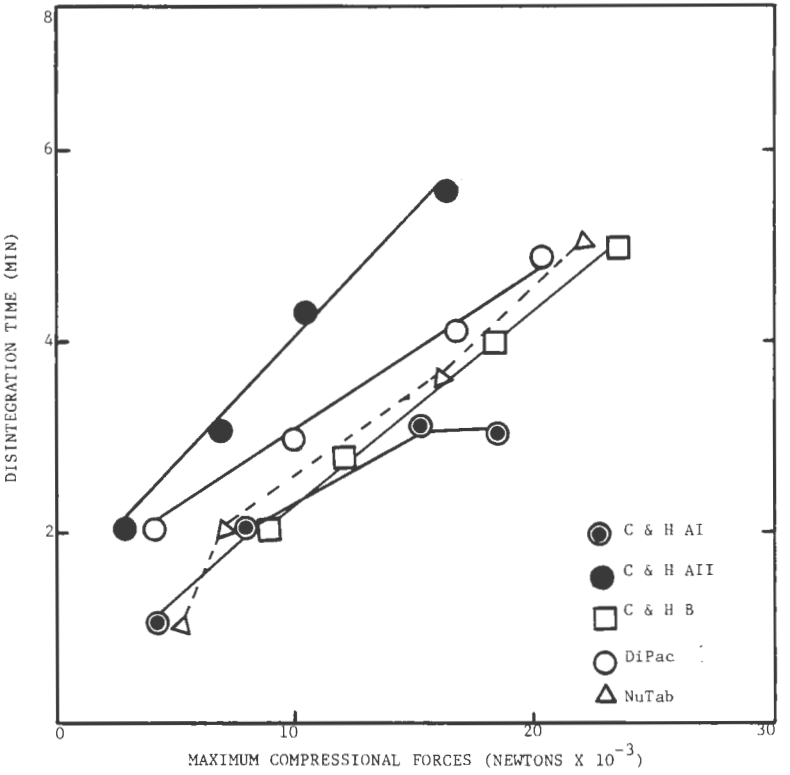


FIGURE 23

DISINTEGRATION AS A FUNCTION OF HARDNESS
(ASPIRIN FORMULATION)

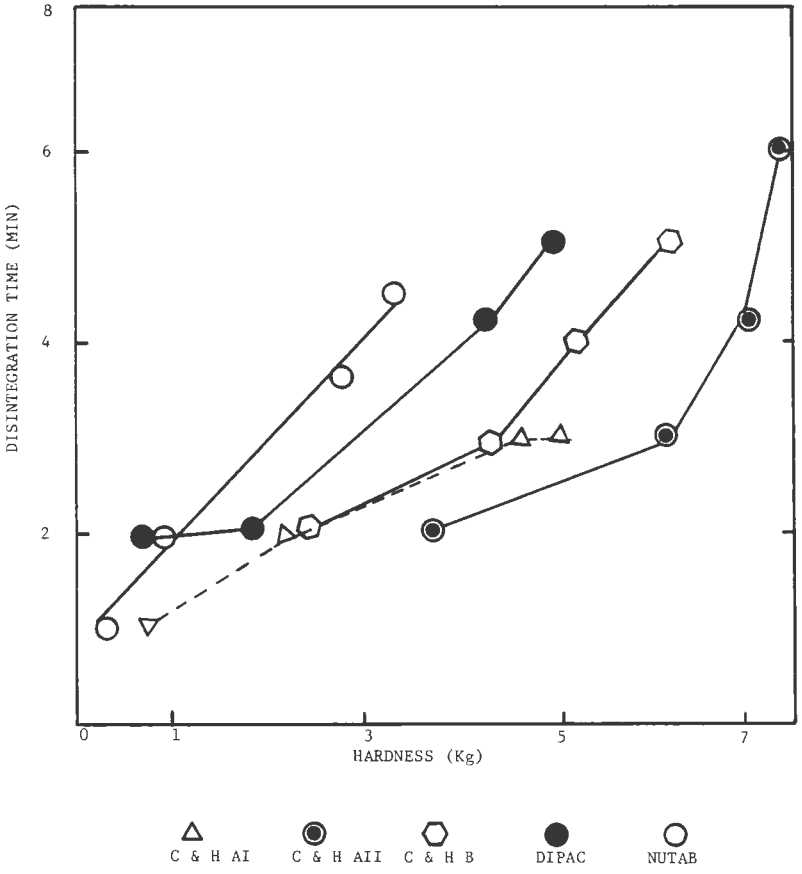
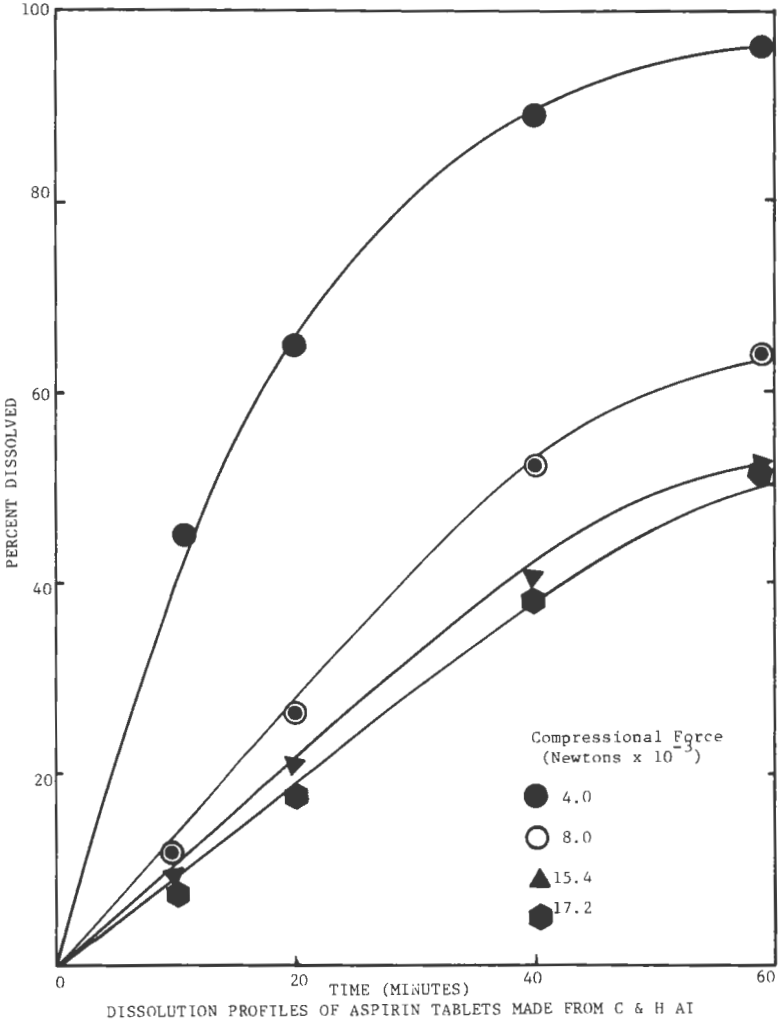
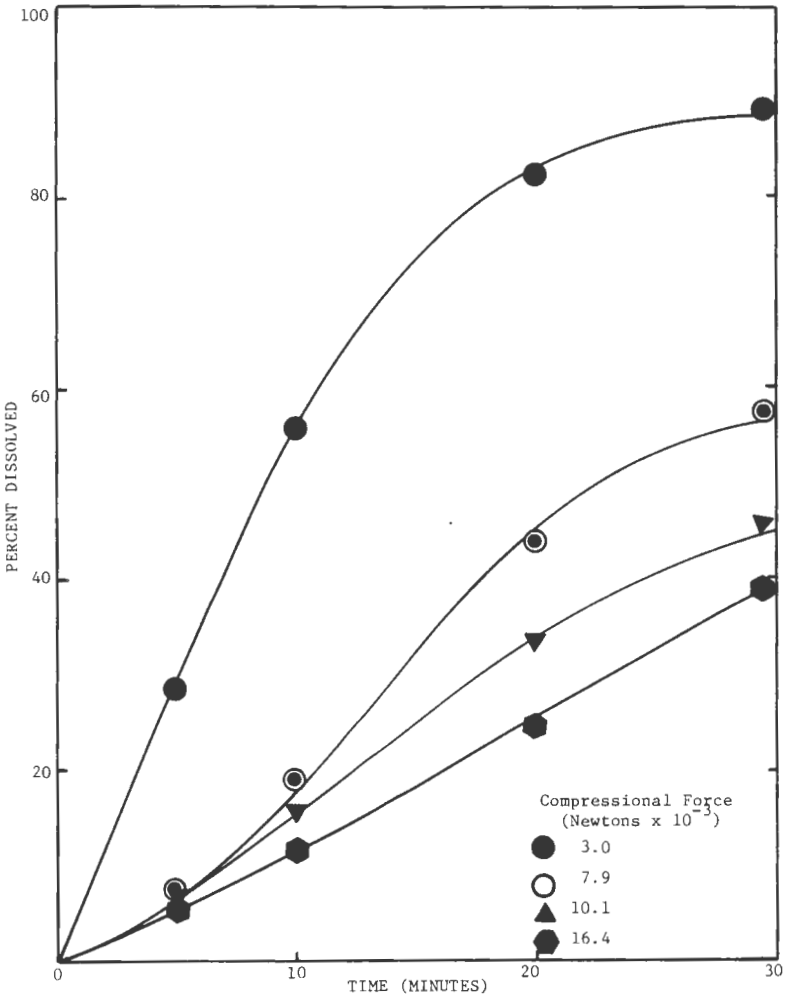


FIGURE 24



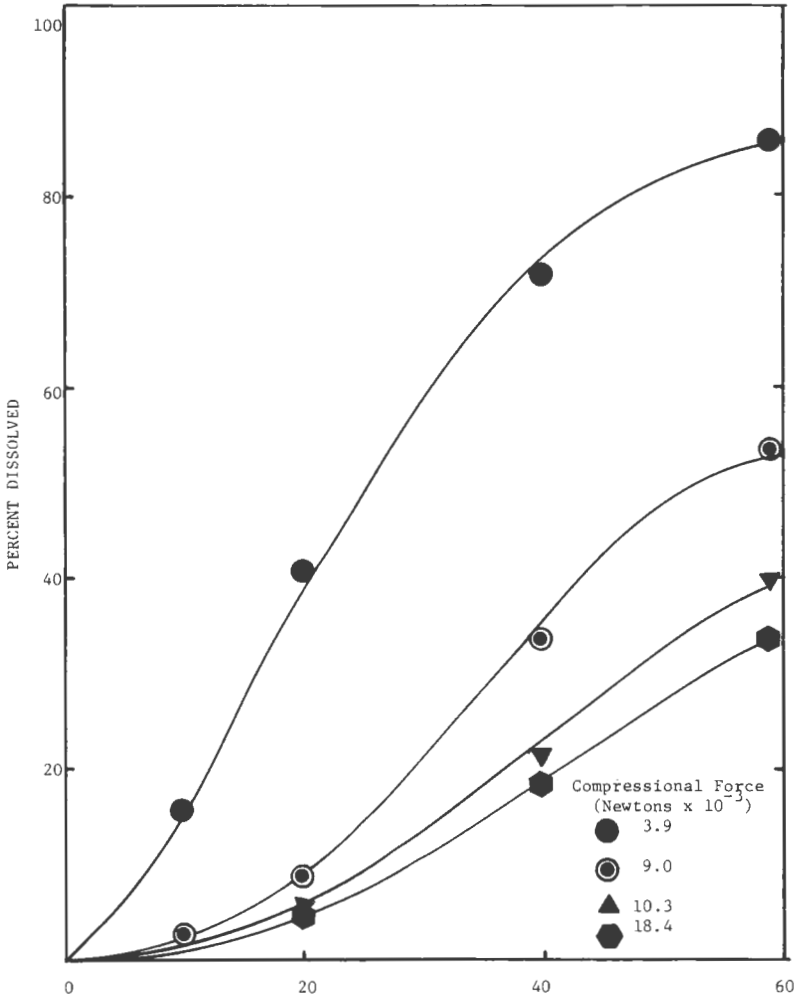
DISSOLUTION PROFILES OF ASPIRIN TABLETS MADE FROM C & H AI
(at four compression levels)

FIGURE 25



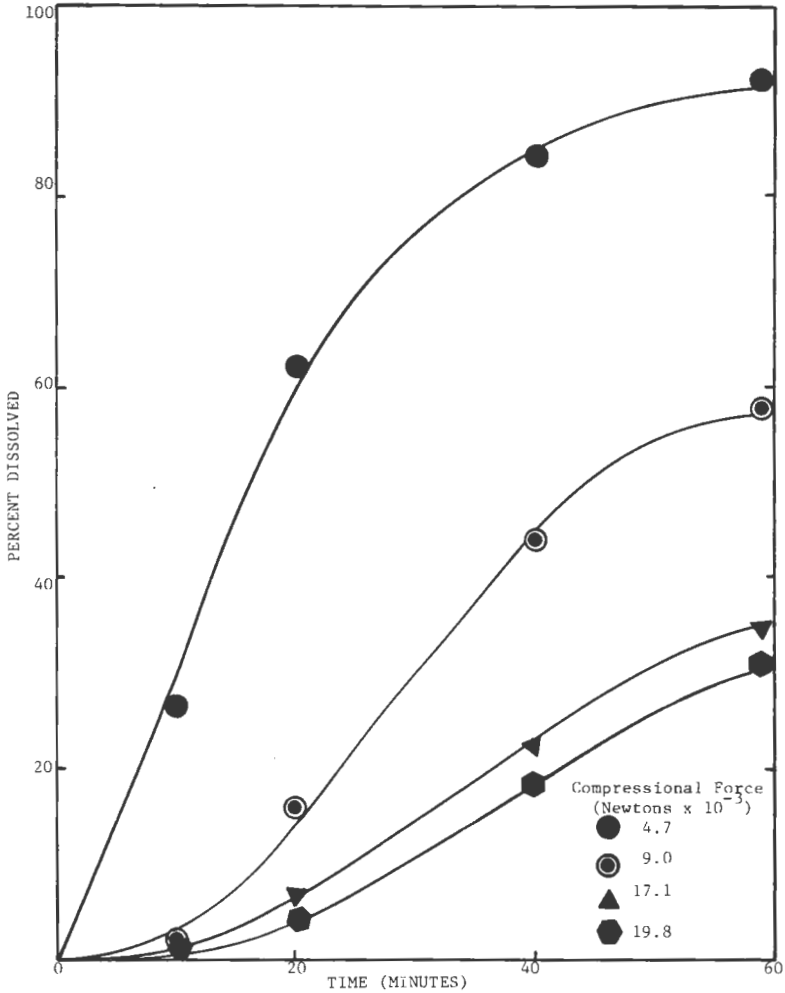
DISSOLUTION PROFILES OF ASPIRIN TABLETS MADE FROM C & H AII
(at four compression levels)

FIGURE 26



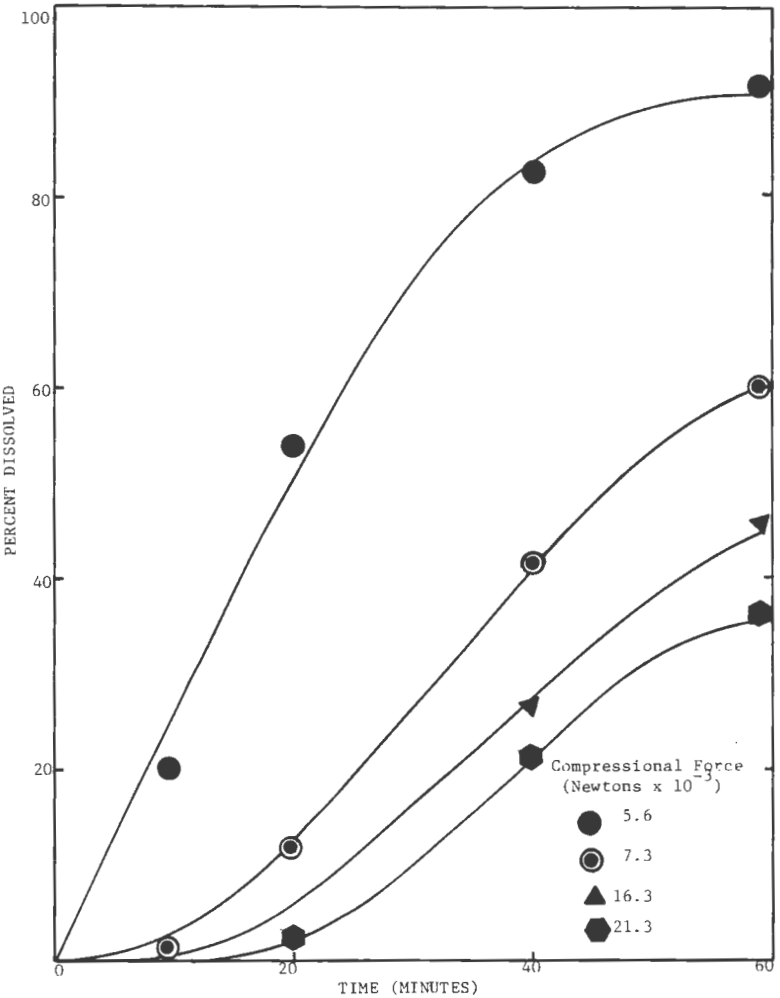
DISSOLUTION PROFILES OF ASPIRIN TABLETS MADE FROM C & H B
(at four compression levels)

FIGURE 27



DISSOLUTION PROFILES OF ASPIRIN TABLETS MADE FROM DIPAC
(at four compression levels)

FIGURE 28



DISSOLUTION PROFILES OF ASPIRIN TABLETS MADE FROM NUTAB
(at four compression levels)

C & H AII, C & H B, DiPac, and NuTab respectively.

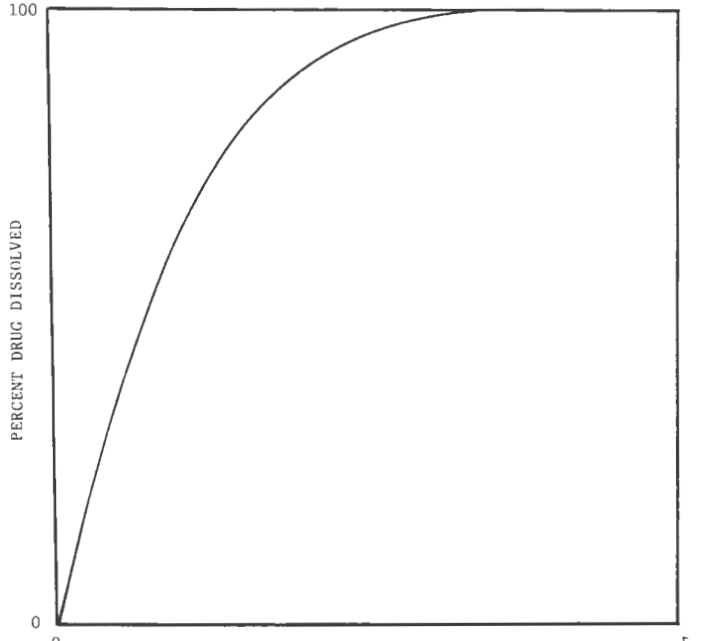
In order to allow the interpretation of the entire dissolution profiles, in relationship to other tablet properties, the concept of "dissolution efficiency" was used. Khan and Rhodes have used this concept to demonstrate the effect of pressure on the dissolution of some direct compression systems (124). In this approach, the area under the dissolution curve at any reference time, t, is divided by the area of a rectangle formed by a line drawn perpendicular to 100% drug dissolved point, and another line drawn perpendicular to the time axis at a reference time point. The ratio of the two areas is then expressed as a percentage, thus, "percent dissolution efficiency" (Figure 29).

Figure 30 shows the effect of compressional force on the dissolution efficiency of the aspirin tablets. A general trend of a decrease in dissolution efficiency with increase in compressional force can be observed.

Figure 31 shows the effect of hardness on the dissolution efficiency of aspirin tablets. A general trend of a decrease in dissolution efficiency with increase in tablet hardness was evident. During the dissolution studies it was observed that at the end of a sixty minute interval, there were appreciable amounts of intact tablet material left at the bottom of the dissolution vessels; as the tablet hardness increased. The material at the bottom of the dissolution vessels appeared to be similar to the aspirin granules used in the formulation. These 'granules' remained intact even when the stirring rate was increased from 50 rpm to 200 rpm, in an attempt to obtain the so-called t_{∞} values. In order to overcome this problem, a long procelain pestle was used to break up the granules, thereby enabling the determination of the total aspirin content of the tablets. Therefore, it is apparent that with increase in compressional

FIGURE 29

DISSOLUTION EFFICIENCY (%)



$$\text{DISSOLUTION EFFICIENCY} = \left(\frac{\text{AREA UNDER THE CURVE}}{\text{AREA OF RECTANGLE}}\right) \times 100$$

FIGURE 30

EFFECT OF COMPRESSIONAL FORCE ON DISSOLUTION EFFICIENCY
(ASPIRIN FORMULATION)

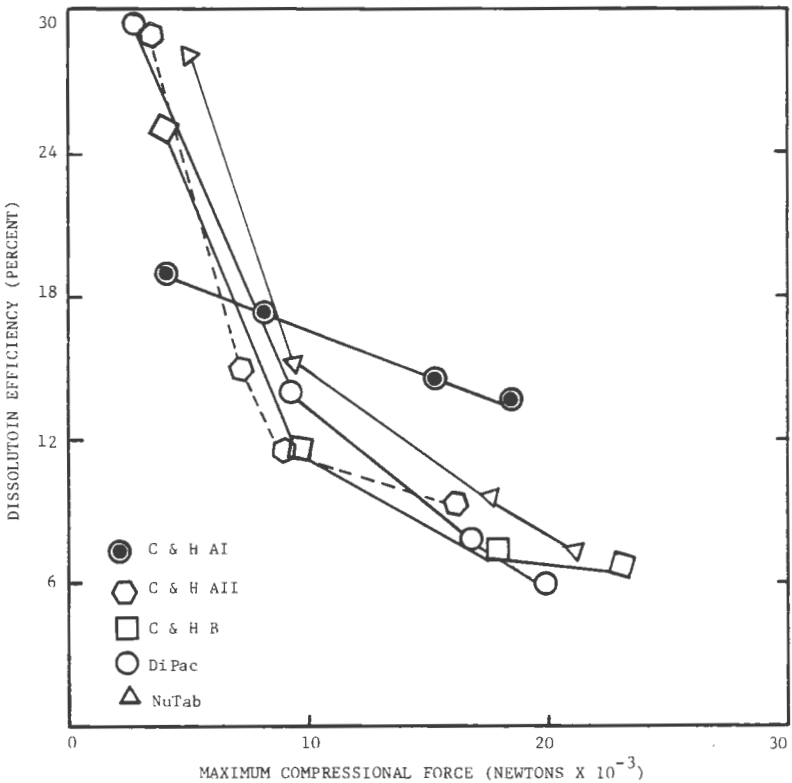
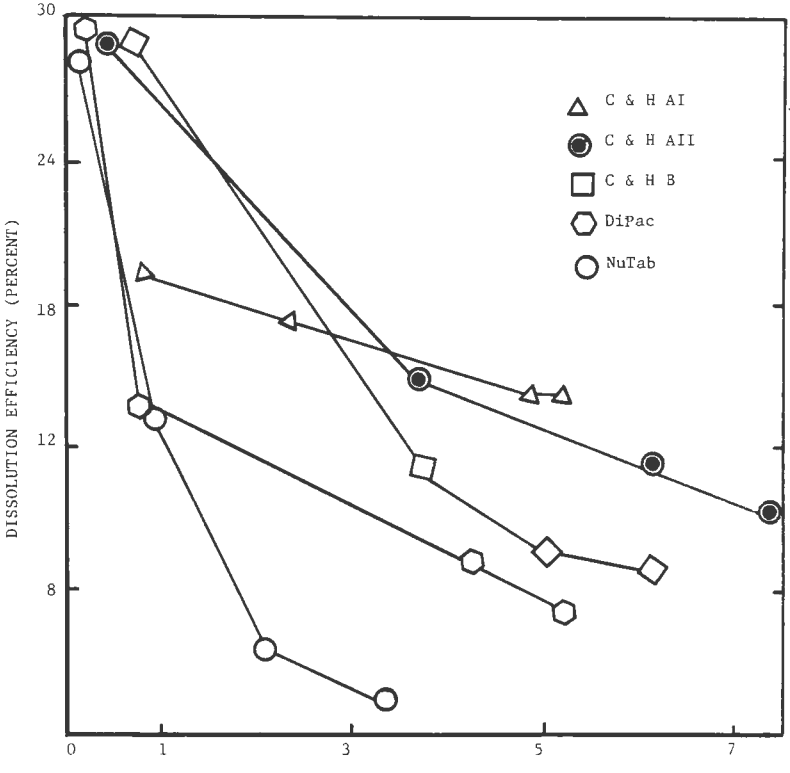


FIGURE 31



EFFECT OF HARDNESS ON DISSOLUTION EFFICIENCY-ASPIRIN FORMULATION

force, there is a corresponding increase in the cohesion of the aspirin-starch granules thus inhibiting the prompt release of the aspirin during dissolution.

Tables XIX and XX show the physical properties of the ascorbic acid tablets made at four different compressional forces. The weight and thickness uniformity were excellent, generally below 1% relative standard deviation. For all the matrices studied, tablet hardness increased with corresponding increase in compressional force. The friability of the tablets decreased with increase in compressional force. In order to facilitate visual inspection of the data, the data pertaining to the physical properties of the ascorbic acid tablets has been presented graphically in Figures 33 through 34.

As would be expected, tablet thickness decreased with increasing compressional force (Figure 32). Figure 33 shows the effect of compressional force on the hardness of the tablets. C & H Product AI produced the hardest tablets, whereas NuTab produced the softest tablets at approximately the same compressional force. All matrices produced tablets that were considerably friable at compressional forces below fifteen thousand Newtons (Figure 34).

Tables XXI and XXII show the physical properties of the multivitamin tablets. C & H AI and AII showed slightly higher variation in tablet weight at low compressional forces. However, the relative standard deviation for tablet thickness remained below 1%. Since the weight adjustment was not altered when the compression settings were changed, the observation can only be explained by variability in the flow rates of the products. The hardness of the tablets increased with higher compressional forces (Table XXII). However, at compressional forces greater than eighteen thousand

TABLE XIX

Physical Properties for Ascorbic Acid Tablets

Matrix Replicate	Compressional Force (Newtons x 10^{-3})	Weight (gm) Mean	Weight (gm) R.S.D.	Thickness (mm) Mean	Thickness (mm) R.S.D.
C & H AI					
1	4.5	1.012	1.54	6.60	0.54
2	7.4	1.004	1.15	6.32	0.28
3	12.9	1.005	0.99	5.99	0.48
4	23.0	1.002	0.99	5.76	0.48
C & H AII					
1	6.1	0.939	4.00	6.47	0.67
2	9.7	0.977	0.80	6.14	0.42
3	16.1	0.965	1.45	5.84	0.41
4	19.1	0.952	1.15	5.58	1.64
C & H B					
1	4.7	0.994	0.66	6.14	0.39
2	12.1	0.996	0.94	5.89	0.54
3	22.8	0.993	0.97	5.53	0.42

TABLE XIX (Continued)

Physical Properties for Ascorbic Acid Tablets

Matrix Replicate	Compressional Force (Newtons x 10^{-3})	Weight (gm) Mean	Weight (gm) R.S.D.	Thickness (mm) Mean	Thickness (mm) R.S.D.
C & H Brown					
1	7.4	1.005	0.48	6.14	0.30
2	9.0	0.996	0.76	5.96	0.41
3	17.1	0.996	0.76	5.94	0.49
4	17.4	0.986	0.44	5.61	0.31
DiPac					
1	9.1	1.024	0.78	6.22	0.28
2	12.1	1.026	0.31	5.96	0.44
3	18.7	1.026	3.41	5.79	0.77
NuTab					
1	10.3	0.991	0.79	5.96	0.53
2	15.2	1.004	0.94	5.79	0.63
3	19.9	0.983	0.66	5.61	0.46

TABLE XX

Physical Properties for Ascorbic Acid Tablets

Matrix Replicate	Compressional Force (Newtons x 10^{-3})	Hardness (Kg) Mean	R.S.D.	Friability Percent
C & H AI				
1	4.5	1.27	25.19	9.90
2	7.4	2.85	15.78	3.60
3	12.9	7.15	12.16	1.18
4	23.0	11.80	10.76	0.71
C & H AII				
1	6.1	1.00	35.00	*
2	9.7	4.10	5.85	1.43
3	16.1	7.50	10.66	0.83
4	19.1	10.12	10.47	0.65
C & H B				
1	4.7	1.25	18.40	*
2	12.1	3.40	13.82	1.80
3	22.8	10.40	9.13	0.60

*

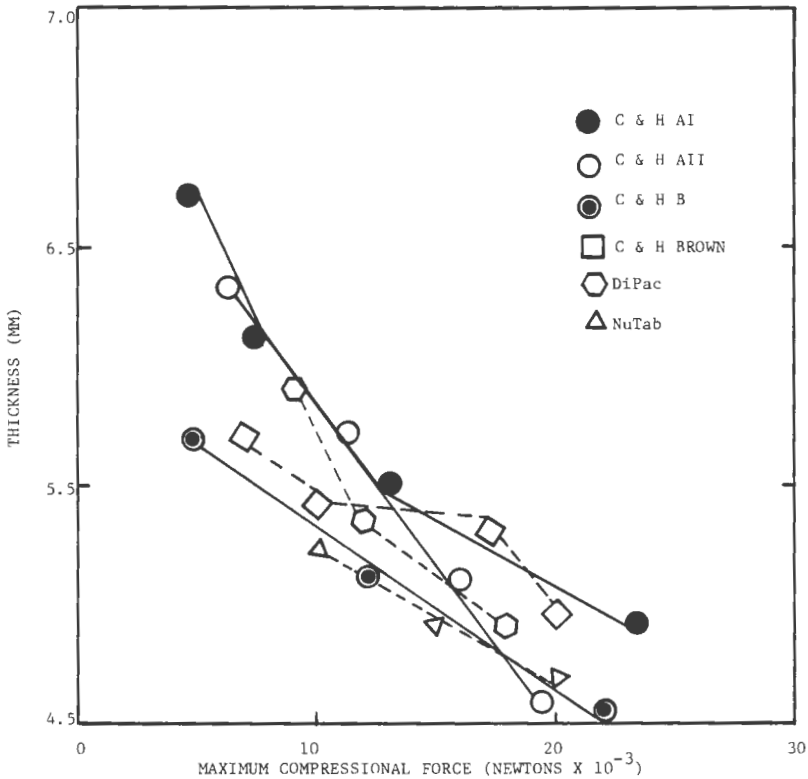
All tablets broke into small pieces

TABLE XX (Continued)

Physical Properties for Ascorbic Acid Tablets

Matrix Replicate	Compressional Force (Newtons x 10^{-3})	Hardness (Kg) Mean	R.S.D.	Friability Percent
C & H Brown				
1	7.4	1.15	18.26	11.00
2	9.90	1.95	27.16	6.20
3	17.1	4.90	9.18	1.30
4	17.4	6.67	8.99	0.80
DiPac				
1	9.1	0.95	26.31	12.69
2	12.1	2.47	11.74	2.03
3	18.7	4.60	21.73	1.17
NuTab				
1	10.3	1.37	19.70	5.25
2	15.2	3.10	11.93	1.80
3	19.9	4.75	21.05	1.04

FIGURE 32



EFFECT OF COMPRESSIONAL FORCE ON TABLET THICKNESS
(ASCORBIC ACID FORMULATION)

FIGURE 33

EFFECT OF COMPRESSION FORCE ON TABLET HARDNESS
(ASCORBIC ACID FORMULATION)

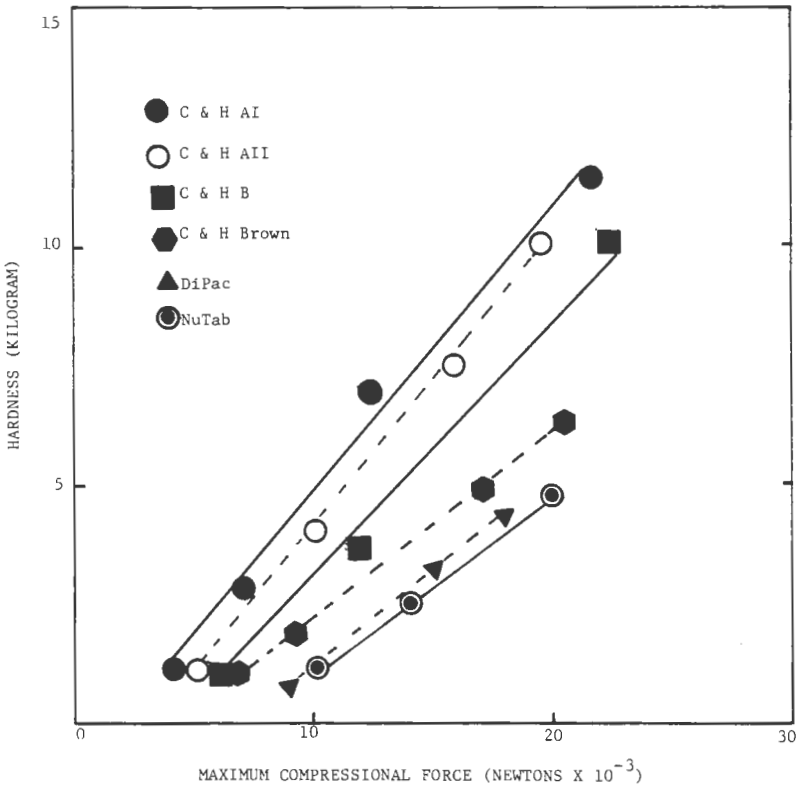


FIGURE 34

EFFECT OF COMPRESSIONAL FORCE ON TABLET FRIABILITY
(ASCORBIC ACID FORMULATION)

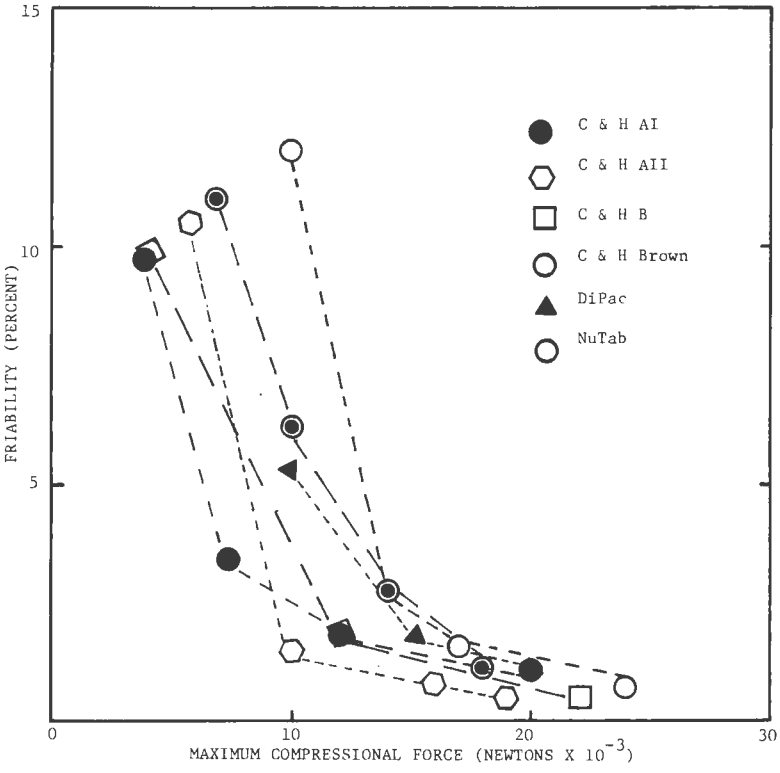


TABLE XXI

Physical Properties for Multivitamin Tablets

Matrix Replicate	Compressional Force (Newtons x 10^{-3})	Weight (mg) Mean	Weight (mg) R.S.D.	Thickness (mm) Mean	Thickness (mm) R.S.D.
C & H AI					
1	1.6	348.5	8.89	5.96	0.50
2	4.5	353.8	0.76	5.53	0.45
3	7.1	350.0	0.79	5.27	0.43
4	12.0	351.6	1.08	5.10	0.64
5	22.3	351.5	0.71	4.97	0.80
C & H AII					
1	2.6	321.5	1.94	5.46	0.65
2	5.2	320.0	1.85	5.02	0.46
3	9.2	323.9	0.75	4.90	0.65
4	15.8	327.2	0.60	4.74	0.46
5	22.7	328.0	0.56	4.72	0.68
C & H B					
1	3.0	344.8	0.32	5.38	0.74
2	4.7	348.0	0.53	5.23	0.42
3	8.3	349.2	0.26	5.08	0.36
4	14.3	349.3	0.23	4.97	0.41
5	22.4	351.3	0.44	4.90	0.43

TABLE XXI (Continued)

Physical Properties for Multivitamin Tablets

Matrix Replicate	Compressional Force (Newtons x 10^{-3})	Weight (mg) Mean	Weight (mg) R.S.D.	Thickness (mm) Mean	Thickness (mm) R.S.D.
C & H Brown					
1	2.5	250.2	0.11	5.48	0.24
2	5.8	350.8	0.51	5.28	0.44
3	11.0	353.0	0.38	5.02	0.61
4	18.8	353.6	0.67	4.92	0.38
5	24.9	355.3	0.32	4.90	0.38
DiPac					
1	3.7	347.0	0.42	5.28	0.50
2	9.5	347.6	0.24	5.13	0.40
3	15.2	345.8	0.35	4.97	0.36
4	19.3	346.9	0.51	4.97	0.48
NuTab					
1	4.0	352.0	0.51	5.46	0.58
2	5.3	351.2	0.25	5.23	0.30
3	10.4	349.7	0.48	5.05	0.42
4	11.1	351.1	0.31	5.08	0.56

TABLE XXII

Physical Properties for Multivitamin Tablets

Matrix Replicate	Compressional Force (Newtons x 10^{-3})	Hardness (Kg) Mean	R.S.D.	Friability Percent
C & H AI				
1	1.6	1.5	18.98	1.14
2	4.5	5.3	11.13	0.35
3	7.1	8.7	10.34	0.28
4	12.0	12.1	14.88	0.21
5	22.3	10.5	12.38	3.30
C & H AII				
1	2.6	3.0	22.66	0.54
2	5.2	7.2	18.05	0.55
3	9.2	9.4	11.70	0.30
4	15.8	13.2	6.05	0.27
5	22.7	10.2	13.91	*
C & H B				
1	3.0	3.0	13.33	0.76
2	4.7	4.8	10.37	0.43
3	8.3	6.9	11.79	0.30
4	14.3	10.0	5.30	0.28
5	22.4	10.5	10.61	0.31

*Significant capping was observed

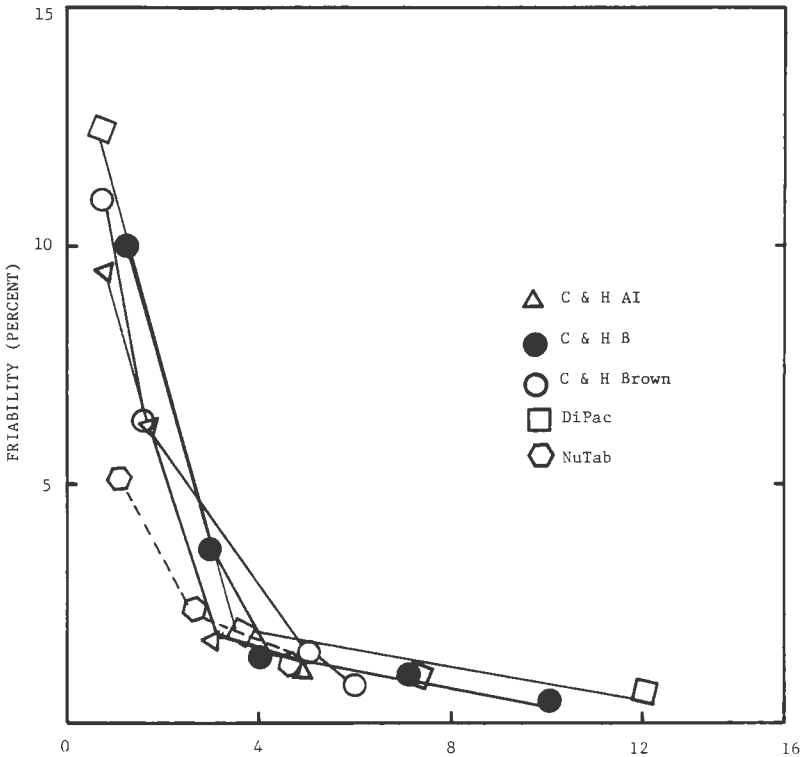
TABLE XXII (Continued)

Physical Properties for Multivitamin Tablets

Matrix Replicate	Compressional Force (Newtons x 10^{-3})	Hardness (Kg) Mean	R.S.D.	Friability Percent
C & H Brown				
1	2.5	1.27	21.25	2.80
2	5.8	3.31	12.72	0.64
3	11.0	9.10	15.30	0.36
4	18.8	12.10	6.61	0.32
5	24.9	10.70	13.50	0.35
DiPac				
1	3.7	2.00	10.00	2.20
2	9.5	3.85	8.05	0.60
3	15.2	7.10	20.56	0.40
4	19.3	5.00	16.00	*
NuTab				
1	4.0	0.88	19.31	0.42
2	5.3	2.70	11.11	0.71
3	10.4	5.20	14.61	0.45
4	11.1	5.90	14.57	1.64

*Significant capping was observed

FIGURE 35



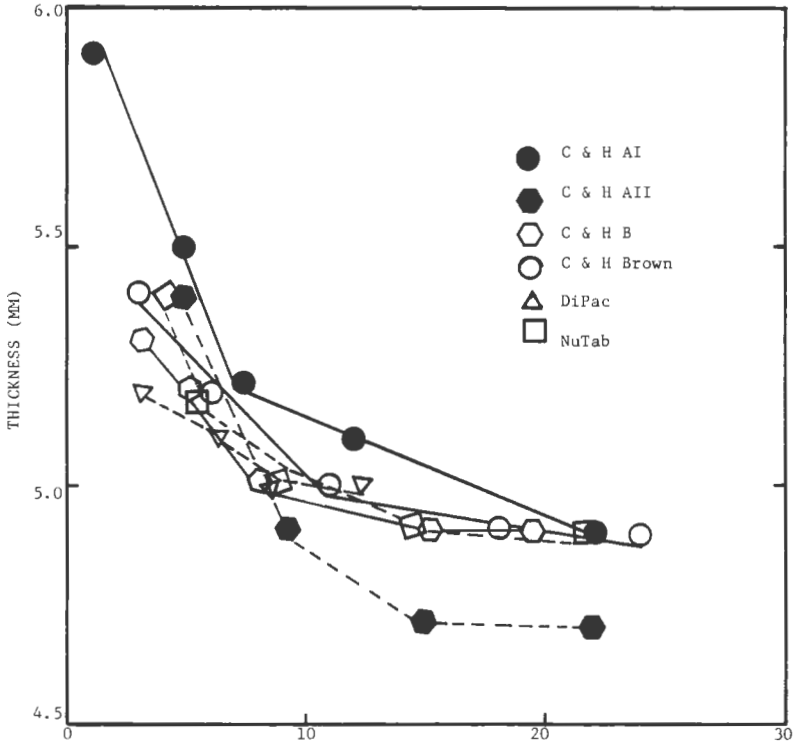
EFFECTION OF HARDNESS ON FRIABILITY-ASCORBIC ACID FORMULATION

Newtons, a decrease in hardness was observed. This corresponded to levels of compression where considerable capping was noted. Figures 36 through 39 represent the data obtained on the Multivitamin tablets. Figure 37 shows the effect of compressional force on tablet thickness. As expected, tablets thickness decreased with increasing compressional force. A special feature with a plot such as one presented in Figure 36 is that it enables one to visualize the compressibility of a powder system. Here, in a relative manner, it can be observed that at compressional forces greater than ten thousand Newtons, C & H AII compressed the most, i.e. had the greatest decrease in tablet thickness.

Figure 37 is a representation of the effect of compressional force on tablet hardness. It was observed that C & H AI and AII had almost identical compressional profiles, producing the hardest tablets, whereas DiPac and NuTab also exhibited similar compressional profiles (producing the softest tablets, at all compressional levels). Those tablets from C & H Product B and the brown matrix showed similar trends.

The friability of the multivitamin tablet decreased with increase in compressional forces (Figure 38). At compressional levels below ten thousand Newtons, there was considerable difference in the friability of the tablets obtained from various matrices. However, when the tablets were compressed at compressional force greater than ten thousand Newtons, no significant difference was observed among the friability values. Figure 39 shows the relationship between hardness and friability of the multivitamin tablets. The differences in friability were only observed at hardness levels below 4 kg. At levels where optimum hardness for most chewable formulations, approximately 7 kg, no significant difference in friability was observed.

FIGURE 36



EFFECT OF COMPRESSIONAL FORCE ON TABLET THICKNESS
(MULTIVITAMIN FORMULATION)

FIGURE 37

EFFECT OF COMPRESSIONAL FORCE ON TABLET HARDNESS
(MULTIVITAMIN FORMULATION)

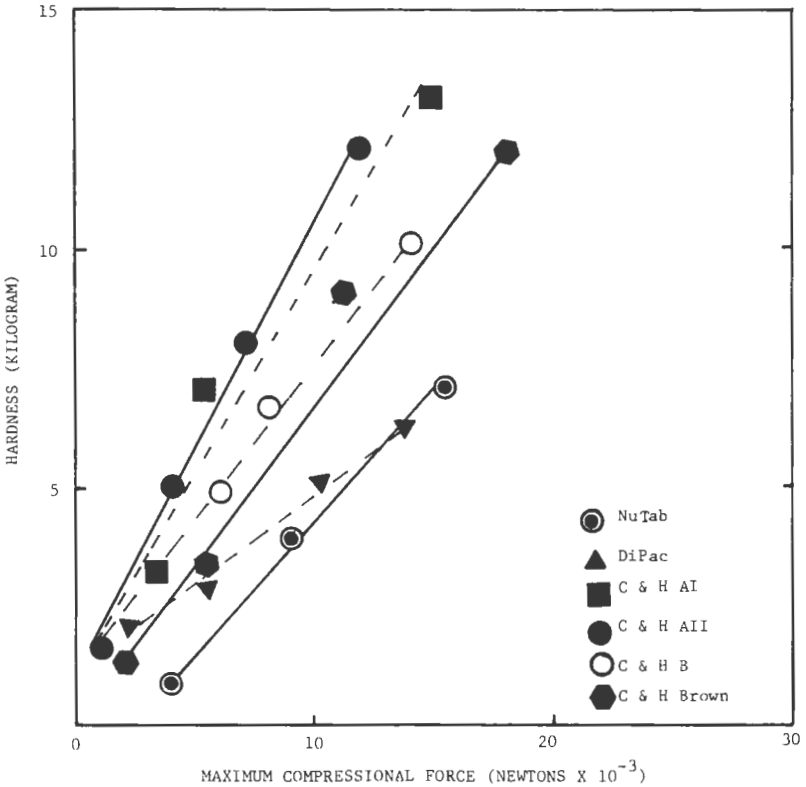


FIGURE 38

EFFECT OF COMPRESSIONAL FORCE ON FRIABILITY
(MULTIVITIAM FORMULATION)

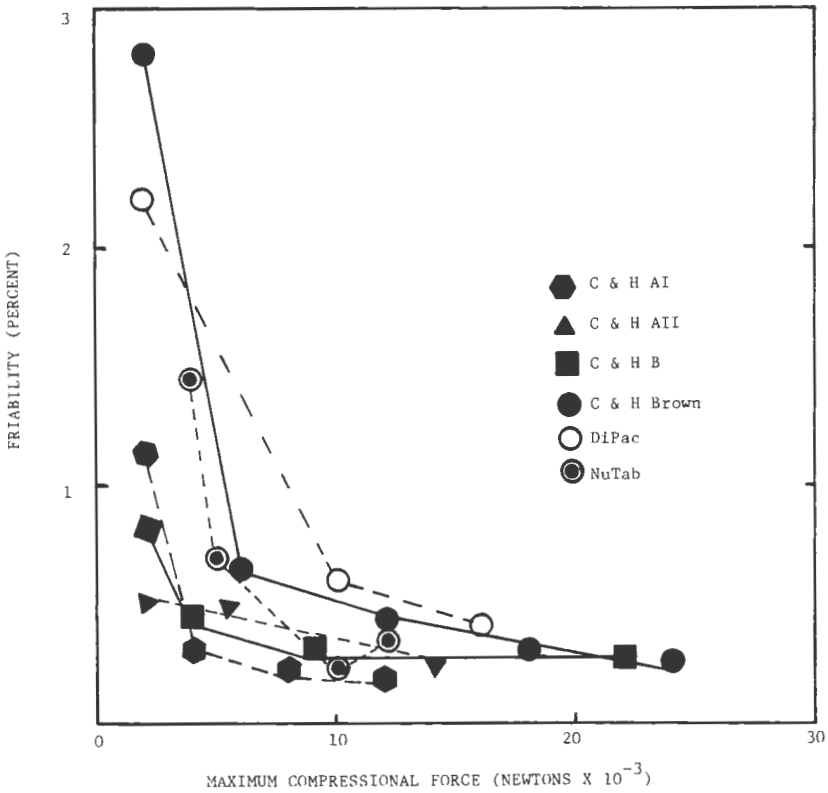
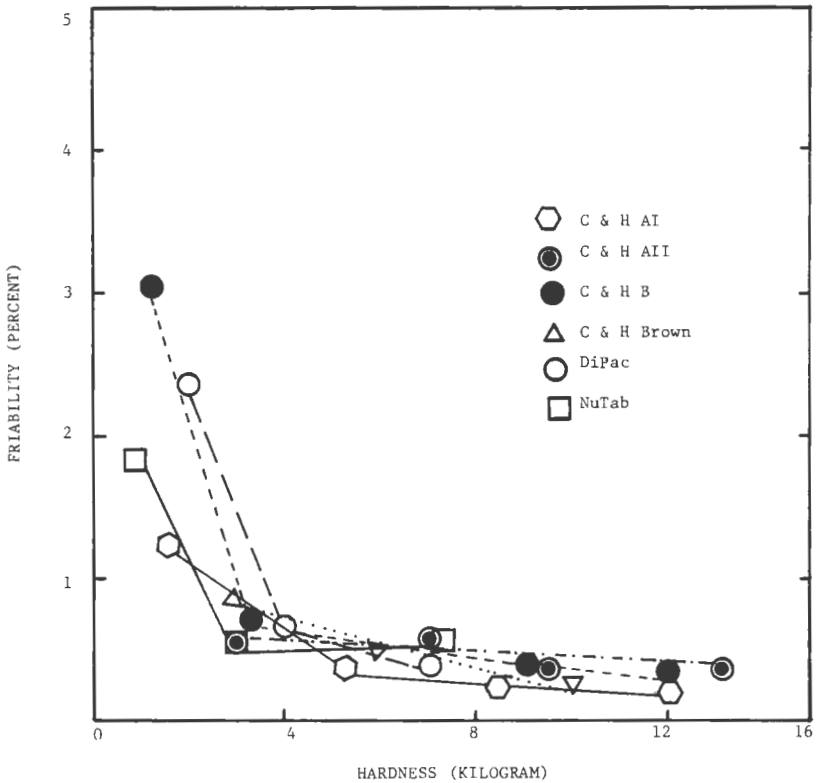


FIGURE 39

EFFECT OF HARDNESS ON FRIABILITY (MULTIVITAMIN FORMULATION)



4. Antacid neutralizing efficiency of direct compression antacids

Antacids are useful in the treatment of acute and chronic upper gastrointestinal disorders. Antacid may be formulated as gums, tablets, lozenges, powders, or liquids. In most cases the liquids, in form of suspensions offer the most prompt relief, particularly in hyperacidity conditions. However, these products are bulky and may be inconvenient to carry. Tablets, particularly, chewable forms, offer an advantage over suspension (especially for pediatric and generiatric groups who find liquids awkward or inconvenient). However, it has been shown that tablets are not equal to liquid antacids on a milligram-for-milligram basis (125).

Although both the USP (1) and BP (85) offer in-vitro methods for antacid evaluation, a review of the literature shows a variety of methods used to evaluate these products. In 1974, the Food and Drug Administration introduced an in-vitro test (86) to determine the antacid-neutralizing rate and the acid-consuming capacity of over-the-counter antacid products. However, it should recognized that although an in-vitro test can approximate in vivo acid-consuming capacity, speed and duration of activity, and maximum buffering capacity of an antacid, other variable such as gastric emptying, changes in the acid secretion rate, interaction of antacid with glycoproteins and mucoprotein of the gastric juice, coating of the gastric mucosa by antacids, and the effect of antacids on the endogenous control of gastric acid sections can not be accounted for (126, 127).

The purpose of this study was to determine the effect of aging on the release of an antacid from water soluble direct compression matrices. Thus, the study was designed to determine the rate and extent of acid neutralization, before and after aging. The various methods for antacid

testing available in the literature can be classified into three main categories: Static, dynamic, and pH-stat. An example of the Static method is that found in the USP XX (1) for the analysis of dried aluminum hydroxide gel. The main disadvantage of this method, is that it provides a limited picture of the entire acid neutralizing process. The dynamic and pH-stat methods provide an approach in following the progress of acid neutralization in a continuous manner. The British Pharmacopiae (85) offers an example of a dynamic method where the pH of an acid medium is measured as a function of time.

In the analysis of acid neutralizing efficiency of the antacid tablets manufactured in the study, a method similar to the British Pharmacopeal guidelines for the analysis of aluminum hydroxide tablets was used. This method is simple, and does not require elaborate equipment. Although it is recognized that as the tablet matrix erodes within the acid medium (intact tablet were used) a suspension- like system forms, and may affect the pH readings, the overall effect is negated as similar test conditions were used for samples tested before, and those tested after aging.

Figures 40 to 48 show the acid neutralizing profiles of the tablet samples studied. The solid lines show the pH-time tracing (and neutralizing profiles) for samples test before aging, and the dotted lines show profiles for samples subjected to one of the aging conditions (ambient, $30^{\circ}C/80\%$ RH cyclic, or $30^{\circ}C/80\%$ RH constant). Tablets samples of C & H AI obtained from all the three storage conditions showed significant change in the acid neutralization profiles (Figures 40, 41, and 42). Only samples stored at $30^{\circ}C$ with 80% relative humidity (constant) showed significant change in the pH-time profiles for C & H B (Figure 45). This trend was also observed for the tablets made from Emdex (Figure 48).

FIGURE 40

ACID NEUTRALIZATION PROFILES OF C & H AI ANTACID TABLETS
STORED AT AMBIENT CONDITIONS

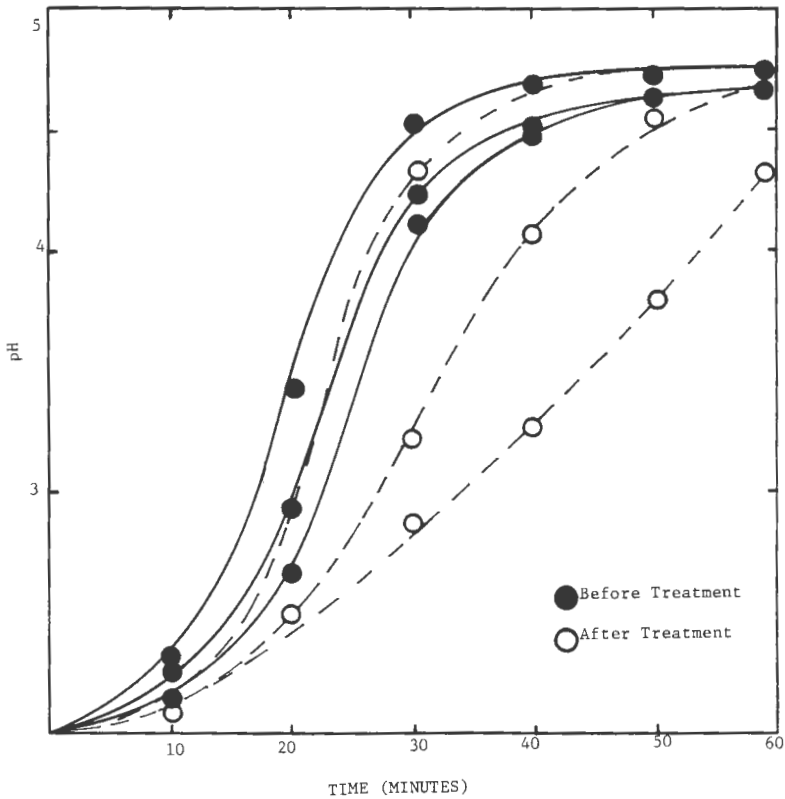


FIGURE 41

ACID NEUTRALIZATION PROFILES OF C & H AI ANTACID TABLETS
SUBJECTED TO CYCLIC STRESS

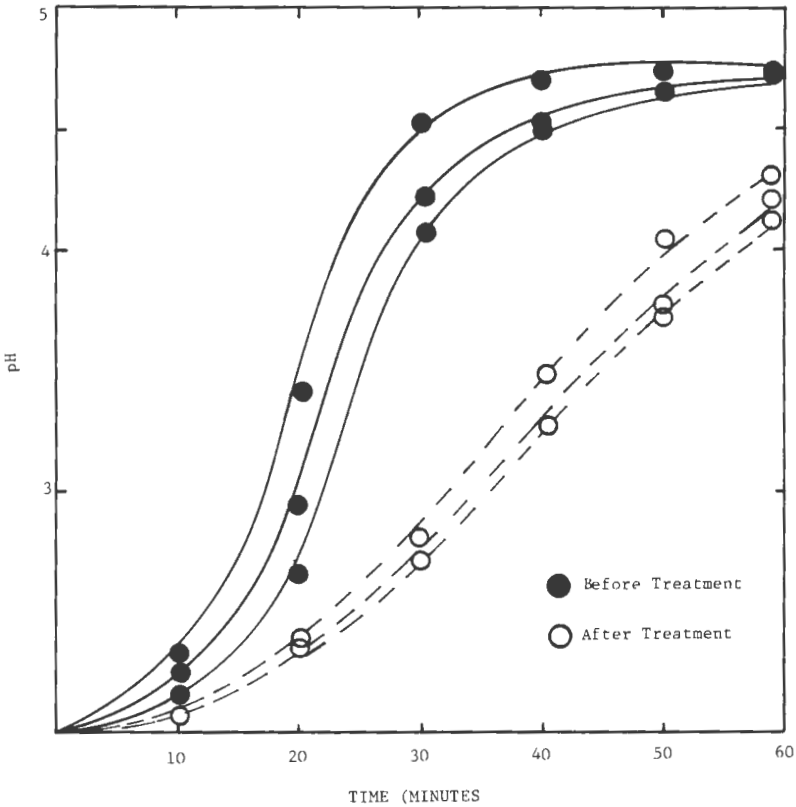


FIGURE 42

ACID NEUTRALIZATION PROFILES OF C & H AI ANTACID TABLETS
SUBJECTED TO CONSTANT STRESS

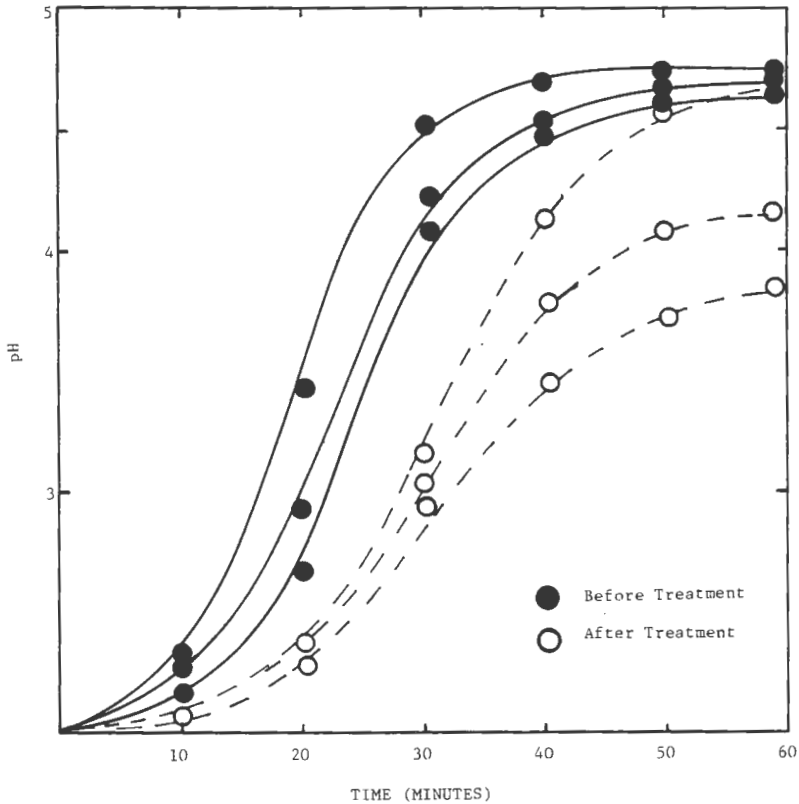


FIGURE 43

ACID NEUTRALIZATION PROFILES OF C & H B ANTACID TABLETS
STORED AT AMBIENT CONDITIONS

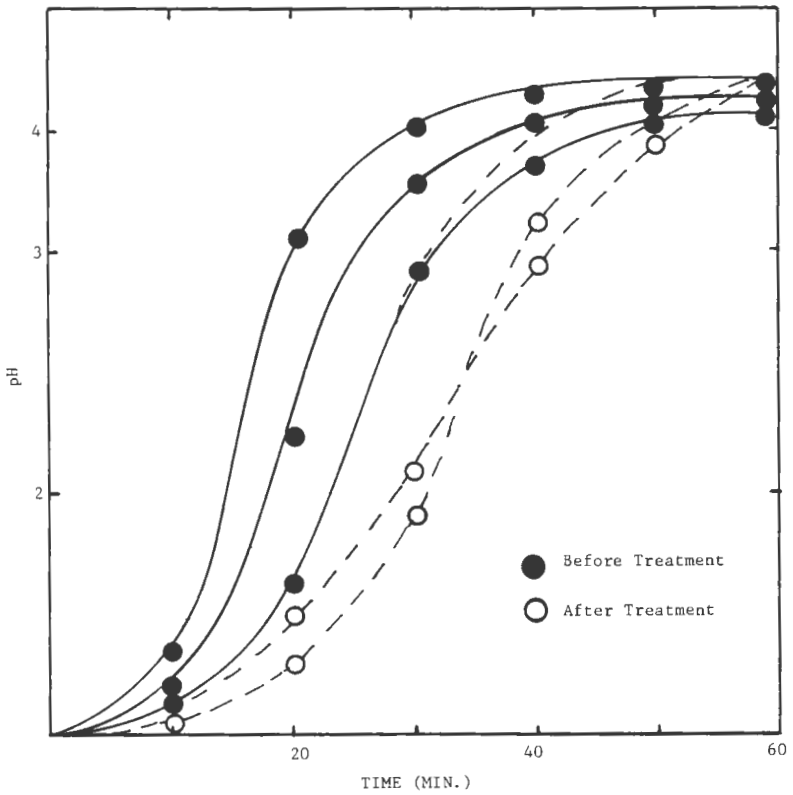


FIGURE 44

ACID NEUTRALIZATION PROFILES OF C & H B ANTACID TABLETS
SUBJECTED TO CYCLIC STRESS

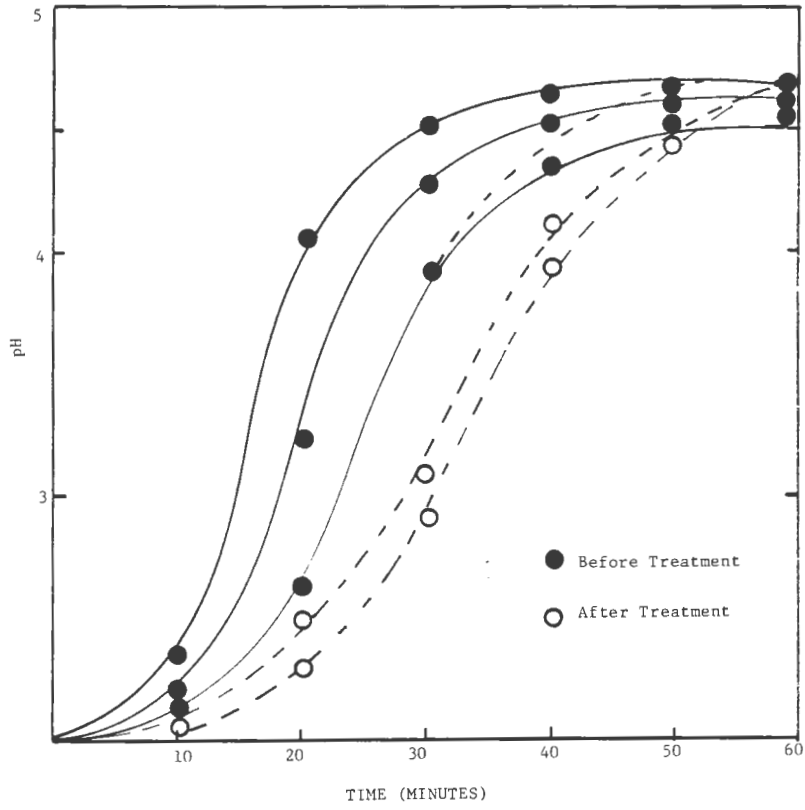


FIGURE 45

ACID NEUTRALIZATION PROFILES OF C & H B ANTACID TABLETS
SUBJECTED TO CONSTANT STRESS

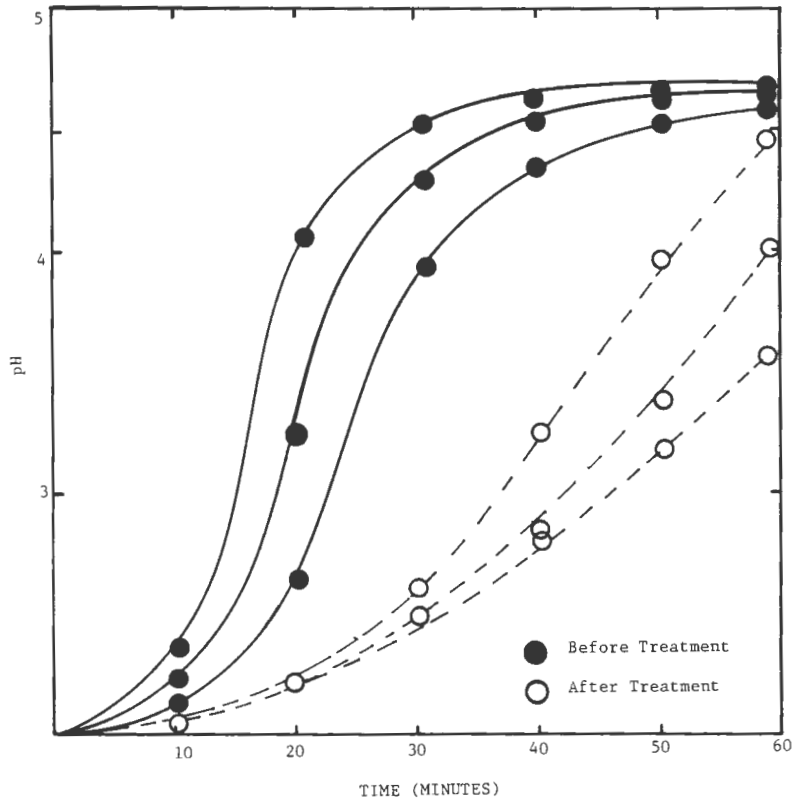


FIGURE 46

ACID NEUTRALIZATION PROFILES OF EMDEX ANTACID TABLETS
STORED AT AMBIENT CONDITIONS

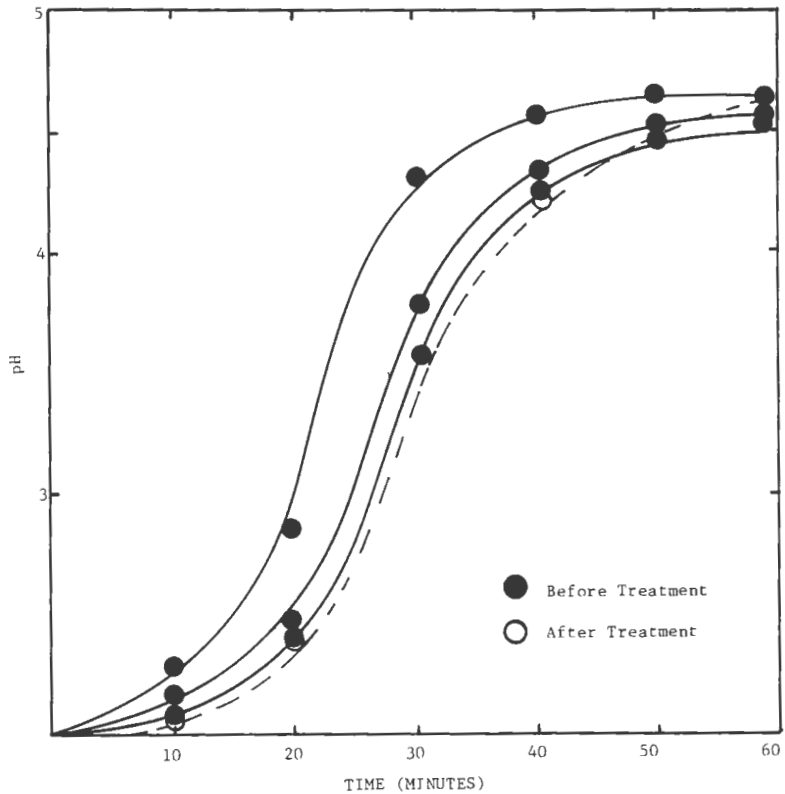


FIGURE 49

ACID NEUTRALIZATION PROFILES OF EMDEX ANTACID TABLETS
SUBJECTED TO CYCLIC STRESS

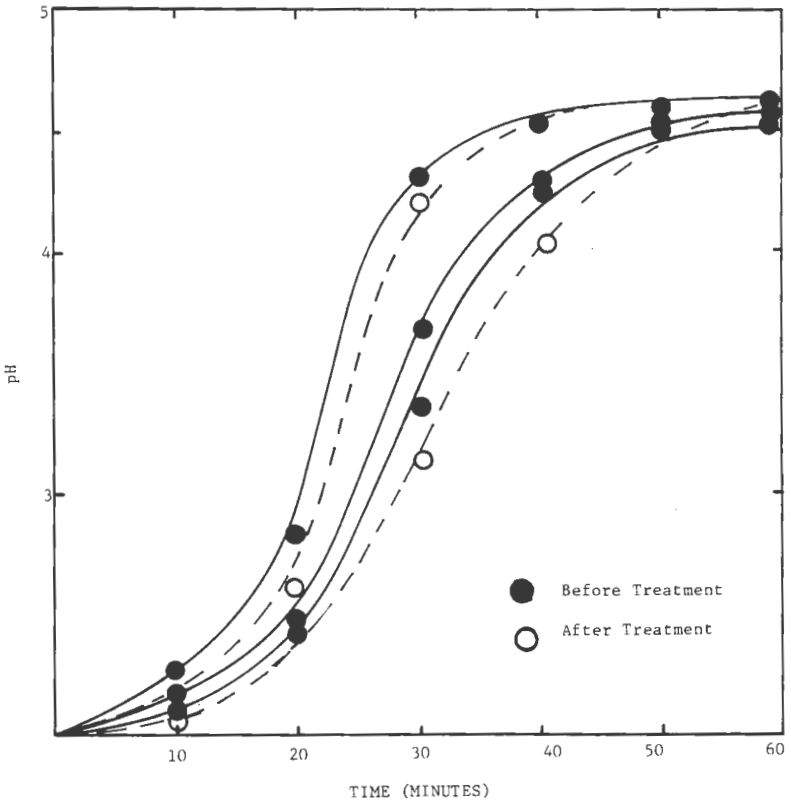
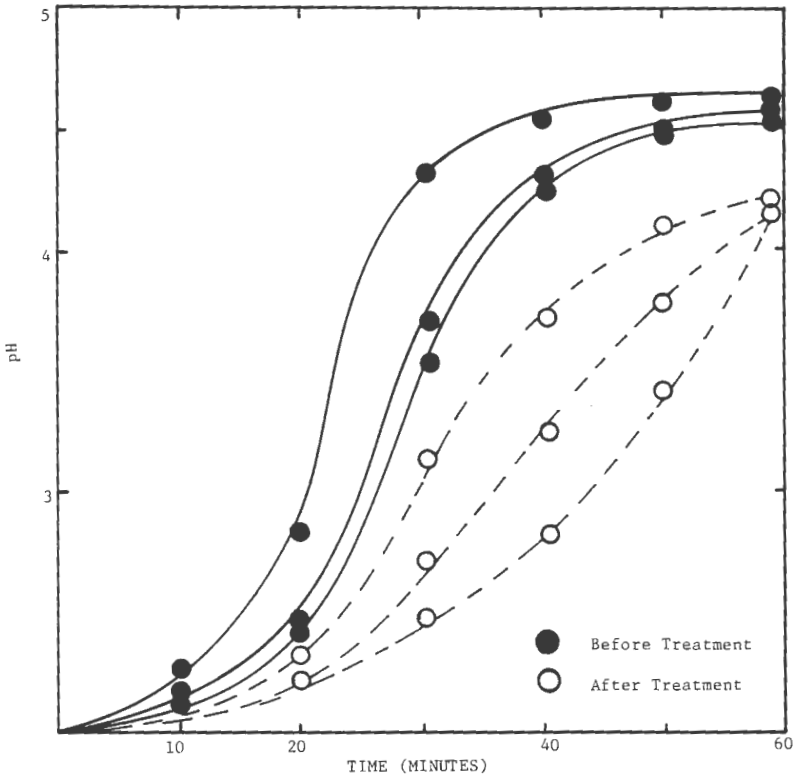


FIGURE 48

ACID NEUTRALIZATION PROFILE OF EMDEX ANTACID TABLETS
SUBJECTED TO CONSTANT STRESS



This study, although conducted over a relatively short period of time (three months), was able to detect appreciable change in the release of antacid material from the tablet matrix. It is therefore quite conceivable that over a prolonged period of time, even at relatively moderate stress conditions, antacid formulated in sugar matrices, may undergo significant aging, perhaps resulting to decrease in-vivo performance.

C. Effect of aging on the disintegration and dissolution of coated tablets

As alluded to in the Introduction Section, the major limitation of sugars as direct compression vehicles, is the high hygroscopicity. Often time, a formulator may circumvent this problem by coating the tablets. Although coating processes such as the application of enteric coating to tablets have been used in industry for a long time, little consideration has been given to the adaptability of such coating to tropical-like conditions.

A study was designed to evaluate the effect of moderate stress conditions on the disintegration and dissolution of several coated tablet products (commercially available). Tables XXIII through XXVI show the disintegration of the tablets studied, before and after aging. A comparison of the dissolution data, evaluated by two methods, i.e. dissolution efficiency approach, and absorbance at various time points, is shown in Tables XXVII through XXX for prednisone (plain, film coated chlorpromazine, sugar coated chlorpromazine, and enteric coated aspirin respectively. Figures 49 through 52 are dissolution profiles of the four products studies.

It is common when designing quality control dissolution specifications, to use one point type tests. For example, "not less than eighty percent of the label claim shall be dissolved in thirty minutes". Although such specifications can be of value for the purpose of batch to batch variation, they are nevertheless limited when investigating dissolution in detail, such as is required in preformulation studies or in investigating tablet aging. Therefore there is considerable advantage in obtaining data which define the entire dissolution curve. The dissolution pattern of sugar coated chlorpromazine in this study exemplifies the need for dissolution data to describe the entire dissolution process (Figure 51). If this had

TABLE XXIII

Effect of Storage on the Disintegration Time of Prednisone

Week	Storage condition*	Disintegration time (range) (Min)
0	A	1 - 1.5
2	B	"
2	C	"
2	D	"
2	E	"
4	B	"
4	C	"
4	D	"
4	E	"

*
A - room temperature, B - 30°C Cyclic, C - 30°C Constant,

B - 30°C/RH Cyclic, 30°C/RH Constant

TABLE XXIV

Effect of Storage on the Disintegration Time
of Film Coated Chlorpromazine

Week	Storage condition*	Disintegration time (range) (Min)
0	A	5 - 8
2	B	5 - 13
2	C	6 - 14+
2	D	5 - 8
2	E	5 - 14+
4	B	5 - 6
4	C	5 - 11
4	D	5 - 11
4	E	5 - 11

*A - room temperature, B - 30°C Cyclic, C - 30°C Constant,
B - 30°C/RH Cyclic, E - 30°C/RH Constant

+Statistically significant from disintegration time for untreated samples

TABLE XXV

Effect of Storage on Disintegration Time
of Sugar Coated Chlorpromazine

Week	Storage condition*	Disintegration time (range) (Min)
0	A	15 - 18
2	B	6 - 7+
2	C	6 - 7+
2	D	6 - 7+
2	E	6 - 7+
4	B	6 - 7+
4	C	6 - 7+
4	D	6 - 7+
4	E	6 - 7+

*
A - room temperature, B - 30°C Cyclic, C - 30°C Constant,

B - 30°/RH Cyclic, E - 30°C/RH Constant

+Statistically significant from disintegration time for untreated samples

TABLE XXVI

Effect of Storage on the Disintegration Time
of Enteric Coated Aspirin

Week	Storage condition*	Disintegration time (range) (Min)
0	A	66 - 68
2	B	66 - 76
2	C	66 - 80
2	D	64 - 98+
2	E	66 - 75
4	B	65 - 78
4	C	67 - 70
4	D	65 - 70
4	E	66 - 69

*
A - room temperature, B - 30°C Cyclic, C - 30°C Constant,

B - 30°C/RH Cyclic, E - 30°C/RH Constant

+
Statistically signficant from disintegration time for untreated samples

TABLE XXVII

Effect of Storage on the Dissolution
of Prednisone 10mg Calibrator

Week	Storage condition*	Prob > t+ Dissolution efficiency	Prob > t Absorbance
2	B	0.53	0.64
2	C	0.05	0.48
2	D	0.09	0.46
2	E	0.09	0.57
4	B	0.74	0.98
4	C	0.41	0.82
4	D	0.15	0.62
4	E	0.62	0.92

*
B - 30°C Cyclic, C - 30°C Constant, D - 30°C/RH Cyclic,

E - 30°C/RH Constant

+
Indicates significance if < 0.05

TABLE XXVIII

Effect of Storage on the Dissolution
of Film Coated Chlorpromazine

Week	Storage condition*	Prob > t+ Dissolution efficiency	Prob > t Absorbance
2	B	0.710	0.87
2	C	0.030	0.61
2	D	0.160	0.52
2	E	0.040	0.49
4	B	0.060	0.88
4	C	0.570	0.34
4	D	0.110	0.99
4	E	0.500	0.23

*B - 30° Cyclic, C - 30°C Constant, D - 30°C/RH Cyclic,
E - 30°/RH Constant

+Indicates significance if < 0.05

TABLE XXIX

Effect of Storage on the Dissolution
Sugar Coated Chlorpromazine

Week	Storage Condition*	Prob > t* Dissolution efficiency	Prob > t Absorbance
2	B	0.0300	0.9900
2	C	0.0030	0.0300
2	D	0.0020	0.6300
2	E	0.1900	0.9900
4	B	0.0800	0.1300
4	C	0.0030	0.0010
4	D	0.0003	0.0003
4	E	0.0010	0.0010

*B - 30° C Cyclic, C - 30°C Constant, D - 30°C/RH Cyclic,
E - 30°/RH Constant

+Indicates significance if < 0.05

TABLE XXX

Effect of Storage on the Dissolution of Enteric Coated Aspirin

Week	Storage condition*	Prob> t+ Dissolution efficiency	Prob > t Absorbance
2	B	0.001	0.320
2	C	0.034	0.0002
2	D	0.480	0.230
2	E	0.094	0.470
4	B	0.460	0.400
4	C	0.001	0.029
4	D	0.390	0.750
4	E	0.350	0.230

*B - 30°C Cyclic, C - 30°C Constant, D - 30°/RH Cyclic,

E - 30°C/RH Constant

+ Indicates significance if < 0.05

FIGURE 49

DISSOLUTION PROFILES OF PREDNISONE TABLETS

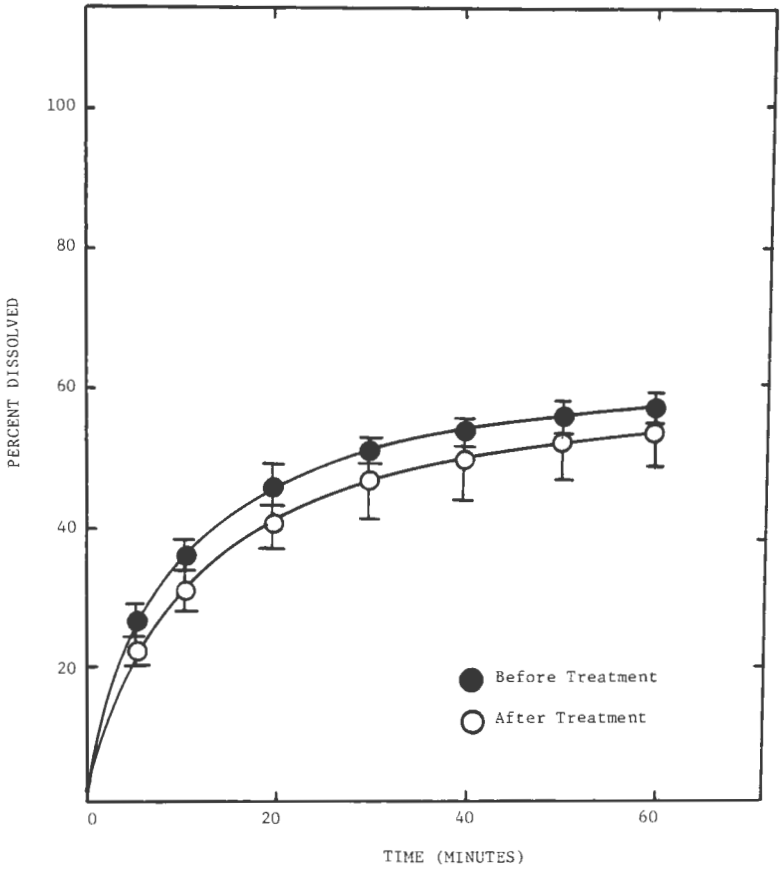


FIGURE 50

DISSOLUTION PROFILES OF FILM COATED CHLORPRAMAZINE

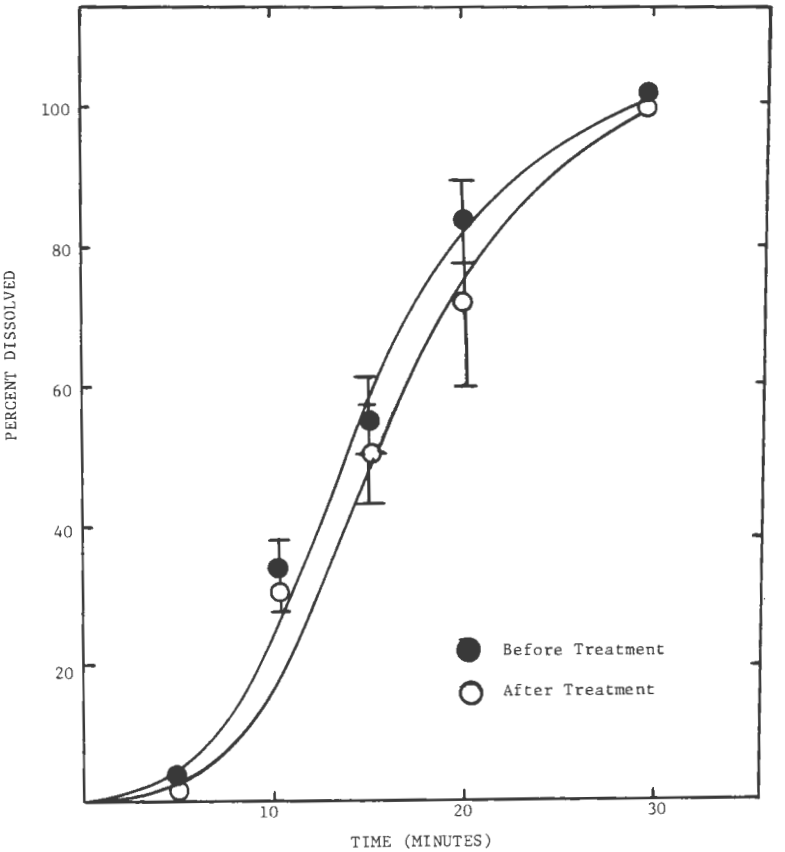


FIGURE 51

DISSOLUTION PROFILES OF SUGAR COATED CHLORPROMAZINE

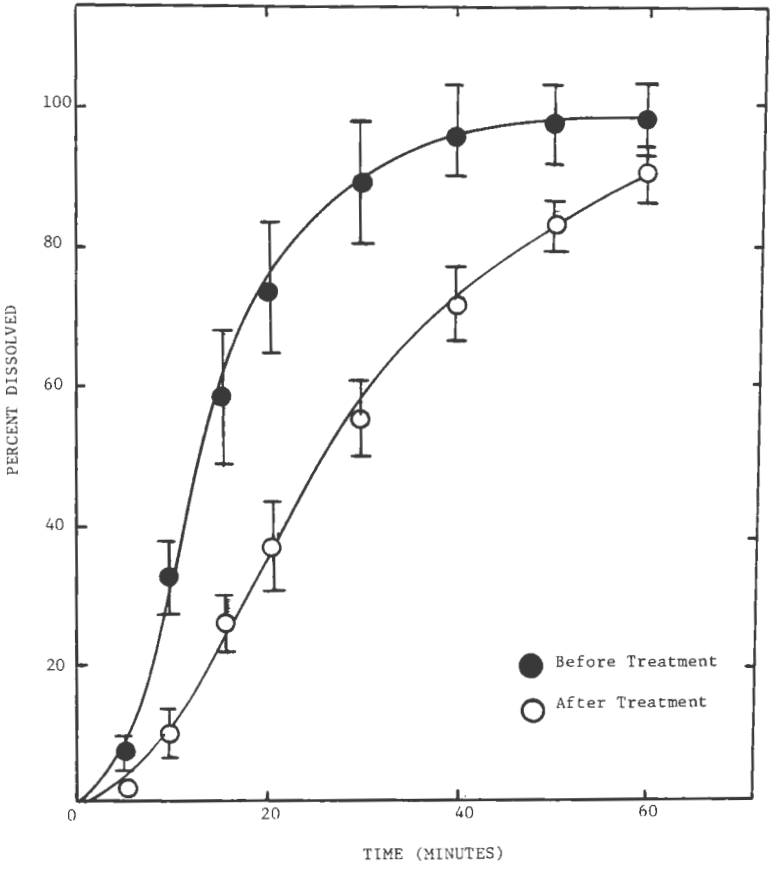
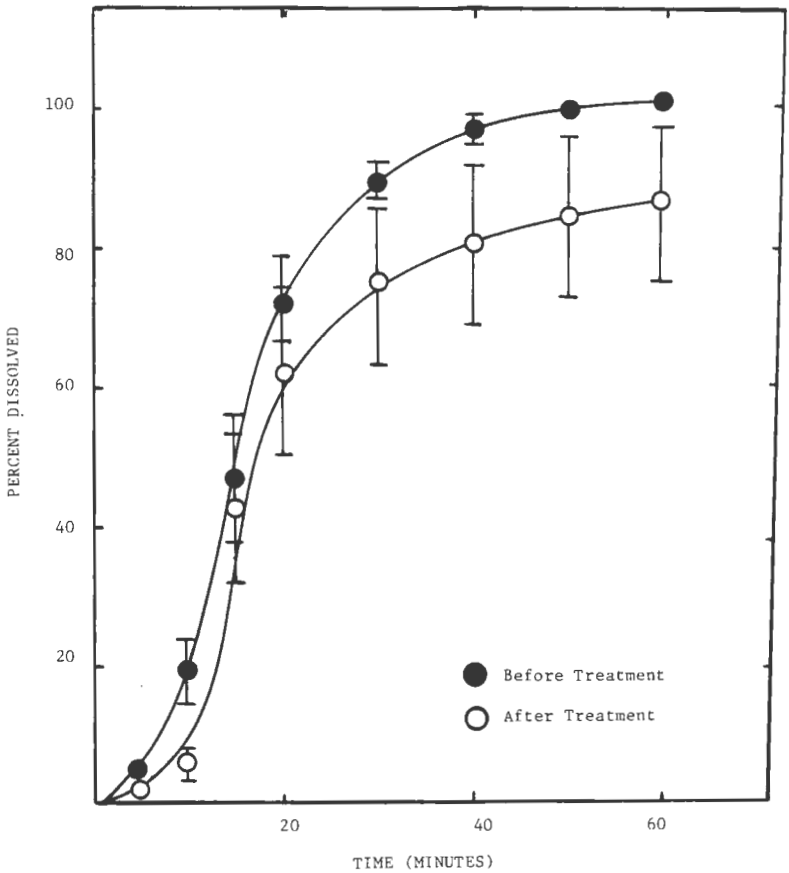


FIGURE 52

DISSOLUTION PROFILES OF ENTERIC COATED ASPIRIN



been restricted to the determination of the percent of drug dissolved at sixty minutes, the conclusion would have been reached that no significant change in dissolution had occurred. However, even simple visual inspection of the entire dissolution curve clearly indicates that storage under stress conditions alters the dissolution pattern of sugar coated chlorpromazine.

In comparing the dissolution profiles for the four products (before and after exposure to the various stress conditions), two methods were used. Firstly, the mean dissolution efficiency (six replicates), as defined by Khan and Rhodes (12) was determined, and the change in this parameter evaluated statistically using Student's t-test. Although this approach offers a convenient method whereby the entire dissolution profiles can be evaluated, "dissolution efficiency" is a derived value, rather than a raw experimental datum. Therefore, a second method of evaluating dissolution data was used. The second method involved a direct comparison of the percent drug dissolved at specific time points using Student's t-test (128).

Both disintegration and dissolution data (Table XXIII and Figure 49) for prednisone showed no significant change. The dissolution profiles (before and after exposure)were virtually superimpossible. This finding suggests that the product is reliable as a dissolution standard.

Results for the film coated chlorpromazine did not indicate any significant change in disintegration and dissolution characteristics. Although the Student's t-test using dissolution efficiency showed a significant change in dissolution for samples stored under 30^{o}C constant, and 30^{o}C/RH constant for two weeks, this difference was not detected when raw data were compared.

Both the disintegration and dissolution data for sugar coated chlorpromazine (Table XXV and Figure 51) showed significant changes as a result of storage. Examining the dissolution profile of this product, it appears that the aging changes are probably associated with the sugar coating rather than the tablet core.

The results of the evaluation of the enteric coated aspirin (Table XXX and Figure 52) showed that the product was susceptable to significant aging. The dissolution of this product is extremely slow even for non-stressed samples. Although the only really conclusive proof that a bio-availability problem exists with enteric coated aspirin would be data from an in-vivo blood level study, these data suggest that enteric coated aspirin has potential for aging problems.

CONCLUSIONS

The following are believed to be the major points of this work as reported and discussed in the previous section.

The new sugar matrices produced by California and Hawaiian Sugar Company (C & H) show considerable potential as direct compression vehicles. In particular, C & H B exhibits the type of flow and compressibility that are essential for high speed tablet production.

Currently, the use of sugar matrices is mainly in the formulation of chewable tablets. However, as demonstrated in this study, if a direct compression matrix has the adequate flow and compressibility, its use can include the formulation of conventional tablets. Although there is increasing concern in some parts of the world, such as in the United States, on the role of sugar in dental decay, the level that is incorporated into a single tablet, for example of 250 mg, is of very little significance; most especially if the tablet is swallowed. Nevertheless, sugar matrices should be used judicially as they may pose a significant problem to diabetics in case where they may take a given formulation repeatedly. At present, sugar is experiencing severe price depression on the world market. This has resulted from a combination of high production and a decline in the use of the product as a sweetener. Many of the sugar producing countries are developing nations. It is thus believed that if the utility of the product was to be expanded (although the pharmaceutical industry would not consume as much tonnage as the beverage industry) this would be an added economic benefit to the producing countries. Faced with foreign currency shortage, partially as a result of high petroleum prices, many developing countries have imposed severe import restrictions. Although in most of

these nations such restrictions have not yet included the very much needed pharmaceuticals, it is conceivable that as world prices of petroleum and other finished goods keep rising, a significant number of these countries may be forced to restrict the importation of pharmaceutical products. One of the solutions to the import problem is to develop a sound domestic program where locally available resources can be fully exploited. The expansion of the use of sugar, particularly in its modified form (suitable for tablet manufacture) is an example of such an effort.

This study demonstrates the importance of raw material specification. When two batches of C & H A (differing only in their particle size distribution spectra) were evaluated, significant differences were observed, both in their intrinsic properties and in their tableting characteristics. Such differences are particularly critical in the production of tablets by direct compression, since little or no change in the material is affected before incorporation into a formulation mixture. However, in wet granulation, through the various steps involved in the process, many inherent ingredient deficiencies may be corrected. The organizations or agencies, such as the United States Pharmacopeal Convention, that are charged with the responsibility of establishing standards for both law materials and finished products (in the pharmaceutical industry) are becoming increasingly aware of the fact that raw material, in different forms, may differ significantly in performance. Such awareness is exemplified in the compendial monographs for some disintegrants. Here, submonographs have been established to reflect the properties of various forms of the raw materials. The data obtained in this study shows the relevance of such specifications. Further, the study shows that a systematic approach can be used to monitor the entire tablet formulation process with relatively

little instrumentation.

Investigation concerning the stability of pharmaceutical products encompass fundamental studies on the rates and mechanisms of the reactions of the active ingredient(s), and the determination of the role of the container, the effect of storage and distribution of the finished production on the integrity of the formulation. A standard approach towards stability evaluation has never been attained in the pharmaceutical industry. Although the stability of most heterogeneous dosage forms can be monitored relatively easily, solid dosage forms, particularly tablets, present a difficult task. Many researchers in the industry employ high temperature and humidity (usually in a constant mode) in an attempt to predict the stability of drug product at room conditions. A great number of the stress conditions currently used do not reflect neither climatic conditions of any region of the world nor actual storage conditions that a drug product could be exposed to. A commonly overlooked fact is that in no geographical region of the world do constant temperature and humidity prevail. The more natural situation, even in the tropics, is one in which temperature and humidity may be high during the day, but drop considerably during night time, i.e., cyclic change. This study compares the effect of both constant and cyclic changes on the stability of tablet formulations, and shows that cyclic storage conditions may indeed be more stressful than constant storage conditions for some formulations.

The results reported in this thesis clearly demonstrate the potential commercial utility of at least one of the C & H Sugars. Further, it is felt that this study helps to substantiate the belief that a rational, logical, largely objective series of tests can be successfully used to evaluate most, if not all, aspects of tablet matrix evaluation.

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APPENDIX

U.S. PATENT INFORMATION ON THE MANUFACTURE OF DI-PAC

United States Patent [19]

Chen et al.

[11] 4,362,757

[45] Dec. 7, 1982

[54] CRYSTALLIZED, READILY WATER DISPERSIBLE SUGAR PRODUCT CONTAINING HEAT SENSITIVE, ACIDIC OR HIGH INVERT SUGAR SUBSTANCES

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[73] Assignee: Amstar Corporation, New York, N.Y.

[21] Appl. No.: 199,553

[22] Filed: Oct. 22, 1980

[51] Int. Cl.³ C13F 3/00; C13F 1/02

[52] U.S. Cl. 426/599; 127/29; 127/30; 127/58; 424/131; 426/650; 426/651; 426/658

[58] Field of Search 127/30, 58; 426/599

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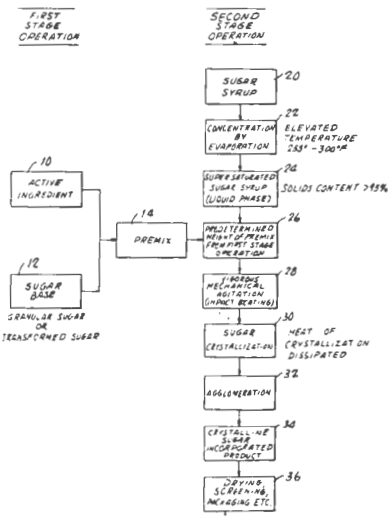
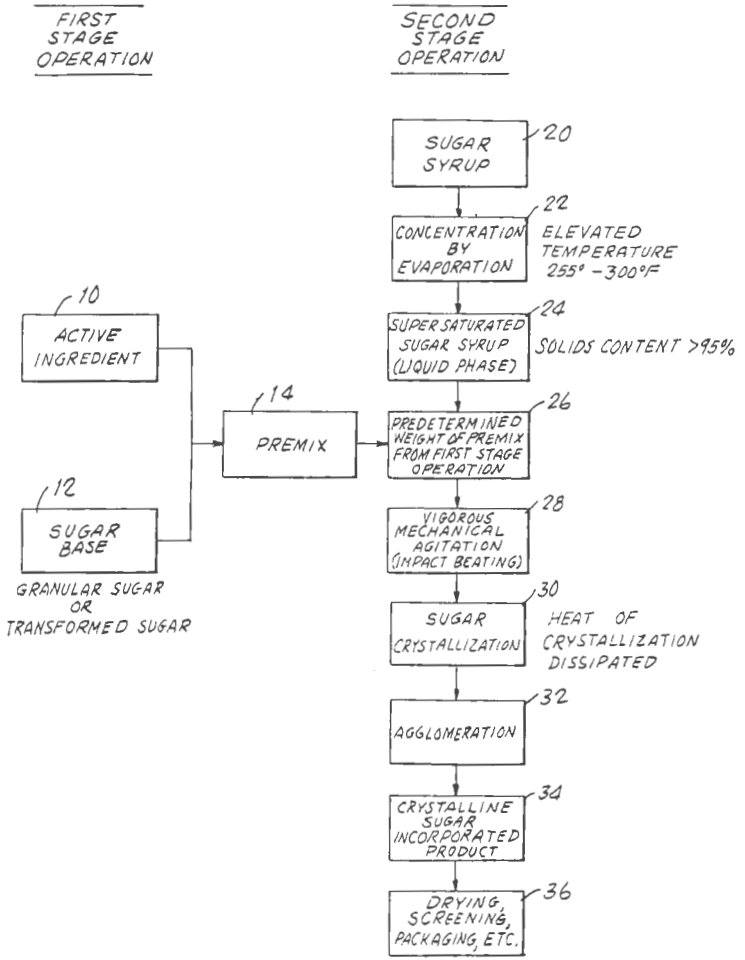
[57] ABSTRACT

A crystallized sugar product containing a heat-sensitive, acidic, or high invert sugar substance is prepared by admixing the heat-sensitive, acidic, or high invert sugar substance with a dry sugar base to form a premix, concentrating a sugar syrup containing at least about 85% by weight sucrose to a solids content of about 95% to about 98% by heating to a temperature of about 255° F. to about 300° F., mixing the premix with the concentrated sugar syrup to form a mixture, subjecting the mixture to impact beating within a crystallization zone until a dry crystallized sugar product is formed, and recovering the sugar product from the crystallization zone. The resulting sugar product comprises aggregates of fondant-size sucrose crystals intimately associated with the heat-sensitive, acidic, or high invert sugar substance. The sugar product is dry, granular, free-flowing, non-caking, and readily dispersible in water.

9 Claims, 1 Drawing Figure




FIRST STAGE OPERATION
SECOND STAGE OPERATION
SUGAR SYRUP
20
CONCENTRATION BY EVAPORATION
22
ELEVATED TEMPERATURE 255° -300°F
SUPERSATURATED SUGAR SYRUP (LIQUID PHASE)
24
SOLIDS CONTENT >95%
10
ACTIVE INGREDIENT
14
PREMIX
PREDETERMINED WEIGHT OF PREMIX FROM FIRST STAGE OPERATION
26
12
SUGAR BASE
GRANULAR SUGAR OR TRANSFORMED SUGAR
VIGOROUS MECHANICAL AGITATION (IMPACT BEATING)
28
SUGAR CRYSTALLIZATION
30
HEAT OF CRYSTALLIZATION DISSIPATED
AGGLOMERATION
32
CRYSTALLINE SUGAR INCORPORATED PRODUCT
34
DRYING, SCREENING, PACKAGING, ETC.
36

CRYSTALLIZED, READILY WATER DISPERSIBLE SUGAR PRODUCT CONTAINING HEAT SENSITIVE, ACIDIC OR HIGH INVERT SUGAR SUBSTANCES

BACKGROUND OF THE INVENTION

This invention relates to a process of producing a granular, free-flowing, non-caking sugar incorporated product. More specifically, this invention relates to a crystallized sugar product which incorporates a heat-sensitive, acidic, or high invert sugar content substance and to a process for making the sugar incorporated product.

In the manufacture of sugar products, a process known as the transforming process is used to produce a dry, granular, free-flowing, non-caking sugar product which is readily dispersed in water. This transforming process has been described in U.S. Pat. Nos. 3,149,682 (Tippens et al.), 3,365,331 (Miller et al.), and 4,159,210 (Chen et al.). In Tippens et al., the method comprises concentrating a sugar syrup to about 95-97% by weight solids hy heating the sugar syrup to a temperature in the range of about 250°-265° F., and immediately subjecting the resulting supersaturated sugar syrup to a heat dissipation operation simultaneously with vigorous agitation. The method produces a dry sugar product comprising aggregates of fondant-size (3-50 microns) sucrose crystals. Miller et al. describes a similar process in which impact beating is used to crystallize the sugar product from the supersaturated sugar syrup.

The feed syrup which is used in the processes of Tippens et al. and Miller et al. has a purity in the range of 85-97% by weight sucrose. Thus, invert sugar (equal portions of glucose and fructose), which has a tendency to cake, may not comprise more than about 15% by weight of the feed sugar syrup.

The sugar products prepared in accordance with the processes of Tippens et al. and Miller et al. are useful as carriers for food additives, such as colorants, flavorants, and pharmaceuticals. The food additives may be introduced into the sugar syrup at either the concentration or the crystallization stage of the processes, depending on the nature of the additive. However, the high temperatures used in the transforming process (about 250°-265° F.) restrict the nature of the food additives which may be incorporated into the final sugar product. Heat-sensitive ingredients, such as volatile flavors or enzymes, cannot be incorporated into the sugar product by the methods described. Further, acidic ingredients, such as Vitamin C or fruit juices, change sucrose into invert sugar by the reaction known as sugar inversion. A further restriction in these processes is that the feed syrup must contain less than 15% by weight invert sugar.

Accordingly, it is an object of this invention to provide a sugar product which incorporates an edible heat-sensitive, acidic, or high invert sugar substance.

It is also an object of this invention to provide this sugar product in granular, free-flowing, noncaking form.

It is also an object to provide this sugar product in a form which is readily dispersed or dissolved in water.

It is a further object of this invention to provide a method of preparing this sugar product.

These and other objects are accomplished by means of the present invention described below.

SUMMARY OF THE INVENTION

By means of the present invention, a crystallized sugar product is produced which incorporates a heat-sensitive, acidic, or high invert sugar substance. The product is dry, granular, free-flowing, and non-caking. The product is composed of agglomerates or aggregates of minute, fondant-size sucrose crystals or particles intimately associated with the active ingredient. Due to its porous structure, the crystallized sugar product is readily dispersed or dissolved in water.

The crystallized sugar product of the present invention is prepared in a two-stage process. In the first stage, a premix is prepared by mixing a dry granular or transformed sugar base with a heat-sensitive, acidic, or high invert sugar substance. In the second or cocrystallization stage, the crystallized sugar product is prepared by concentrating a sugar syrup to about 95-98% by weight solids by heating at a temperature in the range from about 255°-300° F., mixing the concentrated sugar syrup with a predetermined amount of the premix, subjecting the new mixture to impact beating within a crystallization zone until a crystallized sugar product made up of aggregates of fondant-size sucrose crystals and the heat-sensitive, acidic, or high invert sugar substance is formed, the crystallized sugar product having a moisture content of less than 2.5% by weight, and recovering the crystallized sugar product from the crystallization zone. If desired, the resulting crystallized sugar product may be dried to a moisture content of less than 1% by weight, followed by screening to a uniform size and packaging.

DETAILED DESCRIPTION OF THE INVENTION

The accompanying drawing is a flow chart illustrating a preferred process or scheme for preparing a crystallized sugar product in accordance with the present invention.

Referring to the flow chart, the process of the present invention comprises two stages. In the first stage, a premix containing an active ingredient is prepared. The active ingredient **10** in a dry state is blended with a dry sugar base **12** such as a granular or transformed sugar, to form a dry premix **14**. The active ingredient comprises a heat sensitive, acidic, or high invert sugar substance. For example, the active ingredient may be a heat sensitive substance, such as a volatile flavor or an enzyme, or an acidic substance, such as Vitamin C (ascorbic acid) or a fruit juice concentrate, or a high invert sugar substance, such as honey or molasses. The dry sugar base may be pure sucrose or may contain up to about 15% by weight of non-sucrose solids comprising additional monosaccharides, disaccharides, or modified dextrins. For example, the non-sucrose solids may comprise invert sugar, dextrose, fructose, corn syrup, maltodextrins, or mixtures thereof. The amount and type of sugar base which is used may vary depending upon the amount and nature of the active ingredient. The active ingredient is blended with the sugar base, for example, by means of a Hobart Blender, until the desired degree of homogeneity of the premix is achieved.

In the second stage of the operation, cocrystallization of sugar with the active ingredient is achieved. A sugar syrup **20** containing at least 85% sucrose is concentrated by evaporation **22**, under vacuum or under atmospheric pressure, at a temperature in the range of about 255°-300° F., depending upon the nature of the active

material, until the solids content of the concentrated sugar syrup exceeds about 95%. The non-sucrose solids in the feed syrup may comprise additional monosaccharides, disaccharides, or modified dextrins, for example, invert sugar, dextrose, fructose, corn syrup, maltodextrins, or mixtures thereof.

The resulting supersaturated sugar syrup **24** having a solids content exceeding about 95% by weight is maintained at a temperature not less than about 240° F. in order to prevent premature crystallization. A predetermined amount of the premix prepared in the first stage of the process is added **26** to the concentrated syrup with vigorous mechanical agitation or impact beating **28** within a suitable crystallization zone, such as a Hobart Mixer or Turbulizer. Alternatively, the concentrated syrup may be added to a predetermined amount of the premix and mixed in a similar manner.

Impact beating is continued until the resulting supersaturated syrup is transformed, crystallized **30**, and agglomerated **32**. A crystalline sugar incorporated product **34** is recovered from the crystallization zone. The latent heat of crystallization is sufficient to evaporate the moisture so that the product is substantially dry, i.e., has a moisture content of less than about 2.5%. If desired, the crystallized sugar product **34** may be further dried to a moisture content of less than 1%, followed by screening and packaging **36**.

During crystallization, it is desirable to remove the heat of crystallization to prevent overheating within the crystallization zone. The heat of crystallization can be removed or dissipated by indirect heat exchange e.g., by surrounding the crystallization zone with a water jacket, or, preferably, by forced air flow through the beater-crystallizer, e.g., with a vapor separator.

Suitable apparatus for carrying out the process of the present invention is described in U.S. Pat. No. 3,365,331 (Miller et al.).

In order to ensure maximum homogeneity in the final product, it is desirable to introduce the premix into the concentrated syrup as early in the process as practical. However, in most cases, the premix is introduced during the sugar crystallization step in order to prevent deterioration of the active ingredient by the high temperature. The premix becomes thoroughly mixed in the earlier stages of the crystallization step as the concentrated syrup is transformed from the liquid state to a semi-solid state. Consequently, when the syrup reaches the relatively dry agglomerated state, the resulting product is a homogeneous blend of the cocrystallized sugar and active ingredient.

The physical structure of the crystallized sugar product is highly dependent on the rate and temperature of impact beating and crystallization, and on the degree of sugar transformation. The optimum time for the concentrated syrup mixture to spend in the crystallization zone during impact beating depends on several factors including: (a) the nature of the non-sucrose solids (such as invert sugar and ash) in the syrup; (b) the nature and characteristics of the active ingredient (such as moisture content, invert sugar content **pH**, etc.); (c) the concentration of the active ingredient in the premix; and (d) the temperature used for concentration of the feed syrup.

In structure, the crystallized sugar products of the present invention is comprised of aggregates or agglomerates of fondant-size sucrose crystals, e.g., in the range of about 3-50 microns, intimately associated with the non-sucrose solids. The agglomerates form a loose, lacey network bonded together at their interfaces by point contact. Accordingly, aqueous liquid can rapidly penetrate the porous cluster of agglomerates and free each of the particles making up the agglomerates. The particles thus become readily dispersed and/or dissolved in the aqueous liquid.

In the crystallized sugar product of the present invention, the active ingredient is incorporated as an integral part of the sugar matrix and there is no tendency for the active ingredient to separate or settle out during handling, packaging, or storage. The resulting product is granular, free-flowing, non-caking, and is readily dispersed or dissolved in water. Data from a typical analysis of three different sugar incorporated products prepared in accordance with the present invention are presented in Table I.

TABLE I

	Honey Flavored Sugar	Sugar Incorporated Invertase Product	Sugar Incorporated Grape Juice Product
First-Stage Operation:			
(Premix Preparation) Composition	Honey/Sugar	Liquid Invertase/Sugar	Grape Juice Concentrate (68° Brix)/Sugar
(Wt. Ratio)	(1/1)	(1/9)	(3/7)
Second-Stage Operation:			
Composition	Premix/Sugar	Premix/Sugar	Premix/Sugar
(Wt. Ratio)	(2/3)	(1/1)	(1/1)
Elevated Temperature	285° F.	270° F.	290° F.
Solids Content Of Supersaturated Solution (Wt. %)	98.1	97.0	98.5
Finished Product Analysis			
Sucrose (Wt. %)	79.5	94.8	88.65
Invert Sugar Content (Wt. %)	17.2	0.13	9.12
Moisture Content (Wt. %)	0.75	0.45	0.65
Screen Analysis (%)			
No. 28	28.5	18.2	25.8
No. 35	21.7	17.0	24.5
No. 48	25.6	20.5	20.5
No. 65	12.5	17.8	17.6
No. 100	8.6	12.4	9.5
No. 200	2.5	10.0	1.6

TABLE I-continued

	Honey Flavored Sugar	Sugar Incorporated Invertase Product	Sugar Incorporated Grape Juice Product
Pan	0.6	4.1	0.5

A wide variety of products may be made in accordance with the present invention. The following examples illustrate some embodiments of this invention but are not meant in any way to limit the scope thereof.

A flavored sugar product may be prepared by incorporating a flavorant into a crystalline sugar matrix. The flavorants include volatile flavors, such as acetaldehyde or diacetal, nonvolatile flavors, such as natural flavor extracts or artificial flavorings, and essential oils, such as lemon oil or peppermint oil. The product made in this manner provides a fast flavor-releasing character due to the crystalline sugar matrix.

EXAMPLE 1

100 grams of natural peppermint oil in a dry state was blended with 300 grams of granular sugar (Bakers Special Grade) using a Hobart Blender. At the same time, 700 grams of a 65° Brix sugar solution was concentrated at 260° F. to 95% by weight solids content. 300 grams of the peppermint oil-sugar premix was added to the supersaturated, hot syrup with mechanical agitation by an impact beater. Impact beating continued until crystallization occurred and a dry sugar product incorporating the peppermint oil was produced.

EXAMPLE 2

A maple flavored sugar product was prepared according to the process described in Example 1. 100 grams of artificial maple flavor (containing 2.5% maple flavor, FMC6829) was dry-blended with 300 grams of granular sugar (Bakers Special Grade). 300 grams of the premix was added to the hot, supersaturated syrup with impact beating until a dry product was formed.

In another embodiment, a high invert sugar substance, such as honey or molasses, is incorporated into a crystalline sugar matrix. The product made in this manner possesses free-flowing and non-caking properties while retaining a natural delicate flavor.

EXAMPLE 3

200 grams of transformed sugar (Di-Pac ®) was blended with 200 grams of pure honey to form a slurry. 600 grams of a supersaturated sugar syrup, prepared in Example 1, was then added to the premix with agitation. Stirring was continued until the mixture was transformed into a dry sugar product. The product possesses free-flowing characteristics and has a delicate honey taste.

EXAMPLE 4

A product was prepared as in Example 3 using molasses instead of honey.

In another embodiment, a dehydrated fruit juice product is prepared by incorporating a fruit juice concentrate into a crystalline sugar matrix. The resulting product is a free-flowing, nonperishable dry powder which can be used in dry blending formulations.

EXAMPLE 5

100 grams of natural apple juice concentrate (65°Brix) was admixed with 400 grams of granular sugar (Bakers Special Grade) to form a slurry. 777 grams of sugar solution at 65° Brix was heated to 285° F. to form a supersaturated syrup of approximately 98% solids content. The supersaturated sugar solution was added to the premix with impact beating. Impact beating was continued and crystallization proceeded until a dry powdered product was formed.

EXAMPLE 6

150 grams of grape juice concentrate (68° Brix) was mixed with 350 grams of sugar (Bakers Special Grade) to form a slurry. The process continued as in Example 5. The grape juice incorporated product can be used in a grape jelly mix formulation by dry blending with 10.7 grams of pectin.

In another embodiment, a vitamin, such as oxidative vitamin A,C,D,E, or K, is incorporated into a sugar matrix. The resulting product is a homogeneous mixture with high stability. It can be used to fortify other foods.

EXAMPLE 7

10 grams of Vitamin A palmitate (Type 250-SD Hoffmann-LaRoche) was admixed with 390 grams of transformed sugar (Di-Pac ®) to form a premix. 600 grams of a heated, supersaturated sugar syrup, prepared as in Example 1, was added to the premix with mechanical agitation. Stirring was continued until the sugar was transformed and agglomerated into a dry sugar product. One gram of this incorporated product provides exactly 2,500 I.U. of Vitamin A.

In another embodiment, a chemical having beneficial properties, such as ferrous sulfate, dicalcium phosphate, sodium bicarbonate, or a trace mineral is incorporated into a sugar matrix. The product is a homogeneous mixture of the ingredients and can be used to fortify other foods.

EXAMPLE 8

2.08 grams of stannous fluoride was mixed with 297.92 grams of transformed sugar (Di-Pac ®) to form a premix. 600 grams of a heated supersaturated sugar syrup, prepared as in Example 1, was added to the premix with impact beating. Impact beating was continued and crystallization proceeded, eventually resulting in the formation of a dry powdered product. In spite of the high chemical activity and acidity of the fluoride, this chemical was successfully incorporated into the sugar matrix and the resulting product provides exactly 1,000 ppm/gram of the fluoride.

EXAMPLE 9

Example 8 was repeated except that 100 grams of ferrous sulfate was blended with 300 grams of sugar to form the premix. Sugar inversion by the sulfate was avoided due to the present process. The homogeneous iron product can be used to fortify other foods.

In another embodiment, a dry enzyme product or an active culture is produced by incorporating an enzyme, such as invertase, cellulose, glucose, isomerase, amylase, catalase, glucose oxidase, lactase, or pectinase, or an active culture, into a sugar matrix. Notwithstanding the high temperature of the process, the enzyme remains in its active form.

EXAMPLE 10

50 grams of purified invertase in liquid form (Convertit ®, Wallerstein Company) was mixed with 450 grams of transformed sugar (Di-Pac ®) to form the premix. 600 grams of a hot supersaturated sugar syrup, prepared as in Example 1, was added to the premix with mechanical agitation. The agitation was continued until the sugar was transformed, crystallized and agglomerated. The incorporated product (10 grams) was evaluated with respect to its inverting capabilities by blending with various concentrations of liquid sugar (10–40 grams per 100 mls.) and incubated at 30° C. and 55° C. for 1.5 hours. In spite of the high temperature used in the process, the experimental results indicate that a significant portion of the invertase remained active.

In another embodiment, a natural colorant, such as annatto extracts, beet juice concentrates, beta-carotene, grape skin extracts, oleoresin paprika, or tumeric extracts, is incorporated into a sugar matrix. The incorporated product is a homogeneous, stable, dry powder which shows no loss of color strength or hue and which can be used in dry blend formulations.

EXAMPLE 11

100 grams of tumeric color (PT 8-S, Hansen Laboratory) was blended with 400 grams of granular sugar (Bakers Special Grade) to form a premix. 500 grams of heated, supersaturated sugar solution, prepared as in Example 1, was added to the premix with vigorous agitation. The agitation was continued until all the sugar was crystallized. The incorporated product was evaluated for color hue and for color strength (Bexin content). Results showed no significant change in both characteristics despite exposure to the high temperature cocrystallization process.

In another embodiment, an acidulent substance, such as malic acid, fumaric acid, adipic acid, tartaric acid, citric acid, and sodium citrate, is incorporated into a sugar matrix. The resulting product is a free-flowing homogeneous powder which can be used in dry blend formulations.

EXAMPLE 12

The process of Example 11 was repeated using citric acid instead of tumeric colorant.

In another embodiment, an emulsifier, such as lecithin, mono- and diglycericides, propylene glycol esters, sorbitan esters, polysorbate esters, polyoxyethylene sorbitan esters, or lactylated esters, is incorporated into a sugar matrix. The crystallized product permits rapid dispersion of the emulsifier in emulsification applications. The crystallized product, when added to cake mix or icing mix, provides excellent emulsion characteristics. For example, cake volume, porosity, and appearance, and icing stability and density are improved with the sugar incorporated emulsifier as compared with an emulsifier added in the conventional manner.

EXAMPLE 13

100 grams of lecithin (Centrophase C, Central Soya) was mixed with 200 grams of granular sugar (Bakers Special Grade) to form a premix. 800 grams of a heated, supersaturated sugar syrup, prepared as in Example 1, was added to the premix with impact beating. Impact beating was continued and crystallization proceeded, eventually resulting in the formation of a dry powdered product.

EXAMPLE 14

The incorporation method was the same as that used in Example 3, using a monoglyceride (Myverol 18-07, Kodak) instead of lecithin.

In spite of the high temperature employed in the present process, the resulting products are free-flowing, non-caking, dry, homogeneous, stable, non-perishable, and are readily dispersed or dissolved in water.

While the invention has been described with reference to specific embodiments, these were for the purposes of illustration only and should not be constructed to limit the scope of the present invention.

We claim:

1. A method for preparing a cocrystallized sugar product containing an active ingredient selected from the group consisting of heat-sensitive, acidic, and high invert sugar substances, comprising:

(a) admixing the active ingredient with a dry sugar base to form a premix;

(b) concentrating a sugar syrup at a temperature in the range of about 255° F. to about 300° F. to a solids content of about 95% to 98% by weight, said sugar syrup containing no more than about 15% by weight non-sucrose solids;

(c) directly admixing the concentrated sugar syrup at a temperature 255°-300° F. with said premix to form a mixture;

(d) subjecting said resulting mixture upon admixing said premix to impact beating within a crystallization zone until a crystallized sugar product is formed, said crystallized sugar product made up of aggregates of fondant-size sucrose crystals and the active ingredient and having a moisture content of less than about 2.5% by weight; and

(e) recovering said crystallized sugar product from said crystallization zone.

2. The method of claim 1 further comprising drying said crystallized sugar product to a moisture content of less than about 1% by weight.

3. A crystallized sugar product made in accordance with the method of claim 1.

4. The crystallized sugar product of claim 3 wherein the active ingredient is a volatile flavor, a nonvolatile flavor, or an essential oil.

5. The crystallized sugar product of claim 3 wherein the active ingredient is honey.

6. The crystallized sugar product of claim 3 wherein the active ingredient is molasses.

7. The crystallized sugar product of claim 3 wherein the active ingredient is a fruit juice.

8. The crystallized sugar product of claim 7 wherein the fruit juice is orange juice.

9. The crystallized sugar product of claim 7 wherein the fruit juice is grape juice.

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